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Mechanisms Of Reactions Of Alkenesulfonyl And 2-substituted Ethanesulfonyl Chlorides

John Henry Hillhouse

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MECHANISMS OF REACTIONS OF ALKENESULFONYL AND 2-SUBSTITUTED ETHANESULFONYL CHLORIDES

by

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Submitted in partial fulfillment
of the requirements for the degree of
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ABSTRACT

This thesis describes the mechanisms of the reactions of some simple alkenesulfonyl chlorides and 2-substituted ethanesulfonyl chlorides with tertiary amine bases in aqueous and organic media.

Chapter 1 describes the reactions of ethenesulfonyl chloride and trans-1-propene-1-sulfonyl chloride with water in the presence and absence of substituted pyridines. The former reactions are concluded to proceed by S_N2' attack of the pyridine base on the sulfonyl chloride to generate ultimately a pyridine betaine and the pyridinium alkenesulfonate. The formation of the alkenesulfonate anion from the alkenesulfonyl chloride by reaction of the pyridine base corresponds to the first well-established example of a vinylogous nucleophilic catalysis mechanism.

Chapter 2 extends the reactions of ethenesulfonyl chloride and pyridinioethanesulfonyl chloride to include the reaction with pyridine and neopentyl alcohol in an organic medium. Evidence is presented indicating that the reaction of ethenesulfonyl chloride with pyridine in this medium also proceeds by the S_N2' mechanism.

Chapter 3 reports the results of the reactions of a series of 2-substituted ethanesulfonyl chlorides with pyridine and neopentyl alcohol in an organic medium (nitromethane). Three types of reactions which could be correlated with the nucleofugality of the 2-substituent were observed: 1) elimination of the 2-substituent to generate ethenesulfonyl chloride, which then reacts further to generate a [2]betylate and an ethenesulfonate ester; 2) formation of the 2-substituted methylsulfene

intermediate, which then reacts to form an ethenesulfonate ester and a 2-substituted ethanesulfonate ester; 3) formation of a 2-substituted ethanesulfonate ester only, generated from the substituted methylsulfene intermediate.

Chapter 4 presents the first synthesis of an alkanesulfonyl chloride bearing a primary hydroxy group, 2-hydroxyethanesulfonyl chloride. Several reactions of this sulfonyl chloride, including the tertiary amine promoted alcoholysis reactions in methylene chloride, were investigated. The alcoholysis reactions were concluded to be proceeding by the parallel formation of two reactive intermediates, the unsubstituted beta sultone, and 2-hydroxymethylsulfene. The observed reaction products were then derived by further reaction of these intermediates with the components of the medium.

to my parents

ACKNOWLEDGEMENTS

There have been many people who contributed directly and indirectly towards this thesis over the past few years. I thank Dr. J.F. King for his support and guidance throughout the course of this work, particularly during the first and last years. The members of our research group also deserve thanks, especially Dr. S.M. Loosmore, Dr. M. Aslam, J. Lock and M.J. McGarrity whose contributions I am happy to acknowledge.

I wish to thank my friends and parents for their companionship and support during my studies, and Ginny Loeb for typing this thesis.

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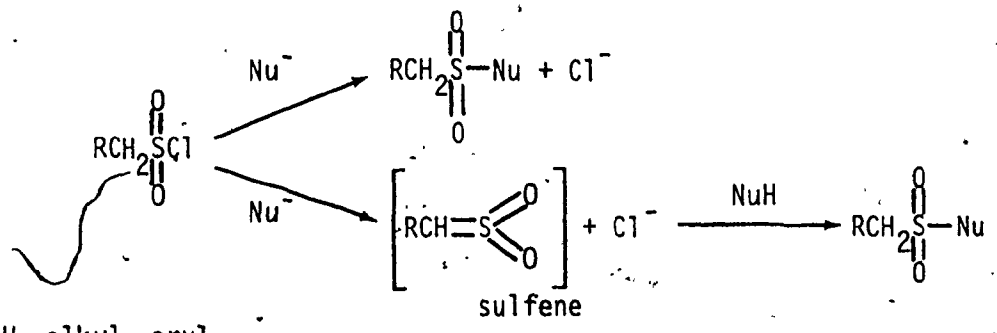
VINYLOGOUS NUCLEOPHILIC CATALYSIS: HYDROLYSIS OF ETHENESULFONYL CHLORIDE AND TRANS-1-PROPENE-1-SULFONYL CHLORIDE IN THE PRESENCE OF PYRIDINE BASES

1:1 Introduction

Sulfonyl chlorides have been useful to the synthetic organic chemist for many years. This has been primarily due to the ease with which sulfonyl chlorides undergo substitution reactions with a variety of reagents to generate useful compounds such as sulfonamides, sulfonate esters, sulfonic acids, and sometimes sulfones (1,2).

There are presently two accepted mechanisms by which an alkanesulfonyl chloride may undergo a nucleophilic substitution reaction. The first mechanism is the direct nucleophilic attack on the sulfonyl group by the added reagent with loss of the chloride ion to generate the observed substitution product (upper pathway in Scheme 1.1). The second mechanism, which was established in the early 1960's by King (3) and Truce (4), takes place by an elimination-addition mechanism involving a sulfene intermediate (lower pathway in Scheme 1.1). The sulfene intermediate in this mechanism was generated by a beta (β) elimination reaction of the sulfonyl chloride, and the substitution product is produced by trapping the sulfene with the nucleophile.

SCHEME 1.1

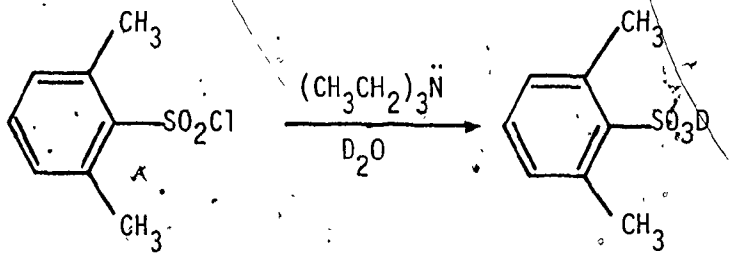


R=H, alkyl, aryl

The elimination reaction of the sulfonyl chloride to form a sulfene intermediate has been well established for a number of aliphatic sulfonyl chlorides (5), and is by far the most important reaction of alkanesulfonyl chlorides when they are treated with tertiary (3°) amines. Sulfenes are very reactive intermediates which are rapidly trapped with a variety of reagents such as water, alcohols and 1° and 2° amines to generate sulfonic acids, sulfonate esters and sulfonamides, respectively. When deuterated trapping agents are employed, most of the observed product is monodeuterated at the alpha (α) carbon (3,4). One example of this reaction is shown below in the formation of a monodeuterated sulfonate ester from a deuterated alcohol and sulfene.

$$\left[RCH{=}SO_2\right] \xrightarrow{R'OD} RCHDSO_3R'$$

For most aromatic sulfonyl chlorides the number of possible mechanisms of substitution is considerably reduced. The reaction of 2,5-dimethylbenzenesulfonyl chloride (1) with triethylamine in deuterium oxide (D_2O), which could in principle react via formation of a sulfene intermediate, apparently does not as judged by the lack of deuterium observed on the methyl groups of the corresponding sulfonic acid (6).



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However, in the light of some very recent work by Williams et al (7) with 4-hydroxybenzenesulfonate esters, a sulfene intermediate derived from a substituted 4-hydroxybenzene-1-sulfonyl chloride substrate remains a distinct possibility.

The hydrolysis of a sulfonyl chloride to a sulfonic acid in the absence of tertiary amines is a general reaction of both aromatic and aliphatic sulfonyl chlorides. Sulfonic acids are often major impurities in samples of commercially available sulfonyl chlorides because of the tendency of sulfonyl chlorides to hydrolyse.

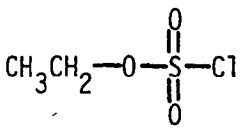
$$R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-Cl + H_2O \longrightarrow RSO_3H + HCl$$

The mechanisms by which sulfonyl chlorides are hydrolysed in neutral and alkaline media have been the subject of a substantial number of publications over the past twenty or more years, with Hambly (8) and Vizgert (9) contributing heavily in this area in the 1950's and 1960's. As a consequence of this work, a large volume of rate data has been accumulated for the uncatalysed hydrolysis reactions of many different aliphatic and aromatic sulfonyl chlorides. This includes pH-rate profiles (log k_ψ versus pH, where k_ψ represents the rate constant for the observed hydrolysis reaction), kinetic solvent isotope effects (KSIE, $k_\psi(H_2O)/k_\psi(D_2O)$) and the usual activation parameters.

For the uncatalysed hydrolysis reaction of an aromatic sulfonyl chloride to the corresponding sulfonic acid, the reaction appears to be a bimolecular substitution reaction at sulfonyl sulfur under most conditions. However, whether the mechanism is a concerted (S_N2)

displacement or involves the generation of a short lived pentacoordinate intermediate is at present an unresolved issue (10). The uncatalysed hydrolysis reaction of alkanesulfonyl chlorides is usually also considered to proceed by the direct substitution mechanism (upper pathway, Scheme 1.1).*

In the late 1950's several chlorosulfonyl derivatives such as ethyl chlorosulfate (2) and 2,4,6-trimethylbenzene-1-sulfonyl chloride (3) were thought to hydrolyse via a sulfonyl cation (RS^+O_2) in an S_N1 mechanism (12,13,14).



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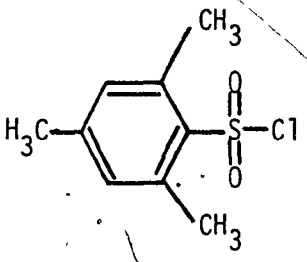

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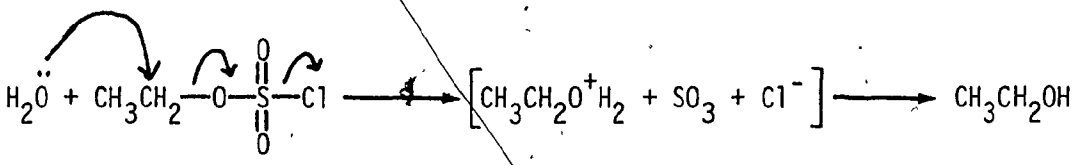
However, due to later research (15,16) with these and several related compounds, the S_N1 mechanism has largely been abandoned for an S_N2 displacement mechanism. For alkyl chlorosulfates generally, a fragmentation mechanism has been proposed (Scheme 1.2).

SCHEME 1.2



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* Preliminary experiments in this laboratory have suggested that the uncatalysed solvolysis of phenylmethanesulfonyl chloride may proceed partly via a sulfene intermediate, as judged by the observation of a small amount of deuterium incorporation at the methylene group of the corresponding sulfonic acid product (11).

The observed hydrolysis rates for most aromatic (17) and aliphatic (18) sulfonyl chlorides appear to be very much pH dependent, with the rate accelerating rapidly as the medium becomes progressively more alkaline. This effect is usually manifested by a pronounced curvature in the pH-rate profile at high pH. This has been attributed to a specific base (hydroxide ion) promoted reaction with the sulfonyl chlorides, since these reactions were found to be first order in sulfonyl chloride and hydroxide ion concentrations. At fairly high pH (~11 or 12) this reaction becomes the dominant pathway for sulfonyl chloride hydrolysis. Aliphatic sulfonyl chlorides may react with hydroxide ion by either mechanism in Scheme 1.1, whereas aromatic sulfonyl chlorides probably react with hydroxide ion via the S_N2 displacement mechanism at sulfonyl sulfur (17).

The effects of electrolytes and the mole fraction of water in the solvent medium upon the rates of the uncatalysed hydrolyses of aliphatic and aromatic sulfonyl chlorides has been determined (8,13). Generally, the electrolytes such as potassium chloride or sodium chloride do not greatly affect the rate of the uncatalysed hydrolysis reaction. For some sulfonyl chlorides the rate appears to reach a maximum at a mole fraction of water (X_{H_2O}) of ~0.95 in aqueous dioxane or acetone solvent mixtures. The reasons for this effect remain unclear, and may be difficult to determine since water is both a reacting species and a solvent in these reactions.

Many reactions in chemistry are catalysed or promoted by the presence of a general acid or a general base. These types of reactions are often best represented by employing a Brönsted catalysis equation. Such equations were developed in the 1920's by Brönsted in order to deal

effectively with catalytic reactions, and these equations are one example of a general class of relationships known as linear free energy relationships (LFER) (19). These relationships have been of great value to the organic chemist in the elucidation of reaction mechanisms.

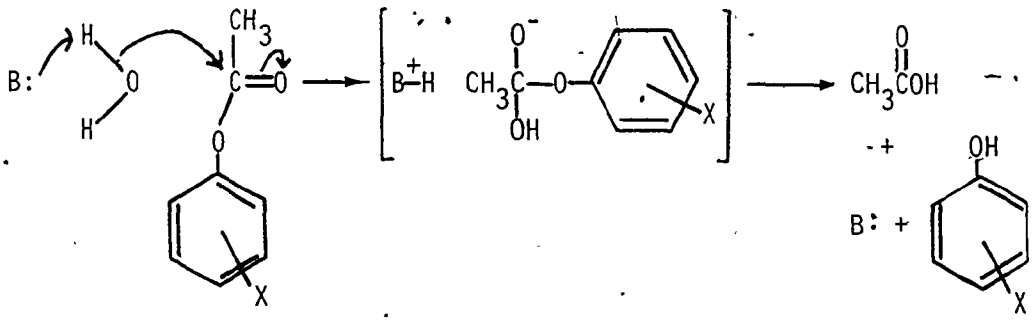
For a general acid catalysed reaction (i.e. a reaction whose rate is observed to be accelerated by the presence of any species which is capable of acting as an acid in the Brönsted-Lowry sense), the Brönsted catalysis equation is $\log k = \alpha \cdot pK_a + C$. For general base and nucleophilic catalysed reactions, the Brönsted equation is $\log k = \beta \cdot pK_a + C$. In both instances k represents the second order rate constant for the reaction of the substrate with each catalyst of known pK_a. Alpha (α) and beta (β) are the Brönsted coefficients which describe the sensitivity of the rate of the catalysed reaction to the series of the acid or base catalysts employed, and C is a constant. Most of the emphasis in this thesis will be upon general base and nucleophilic catalysed reactions of sulfonyl chlorides. For both general base and nucleophilic catalysed reactions the rate of the reaction of the substrate is dependent upon the concentration of all free bases in solution with the substrate: $\text{rate} = k_1[\text{substrate}] + \sum k_{Bi}[Bi][\text{substrate}]$ where [Bi] is the concentration of free base i and k_1, k_{Bi} are the rate constants for reaction of the substrate with the the solvent (water in aqueous solutions) and free base i, respectively.

Since a base may in principle act either as a base or a nucleophile, it is not unreasonable to expect to encounter reactions where a base is acting as a nucleophile in the kinetically significant step. Hence the distinction between general base and nucleophilic catalysis has become necessary. These two mechanisms are illustrated in Scheme 1.3 for the

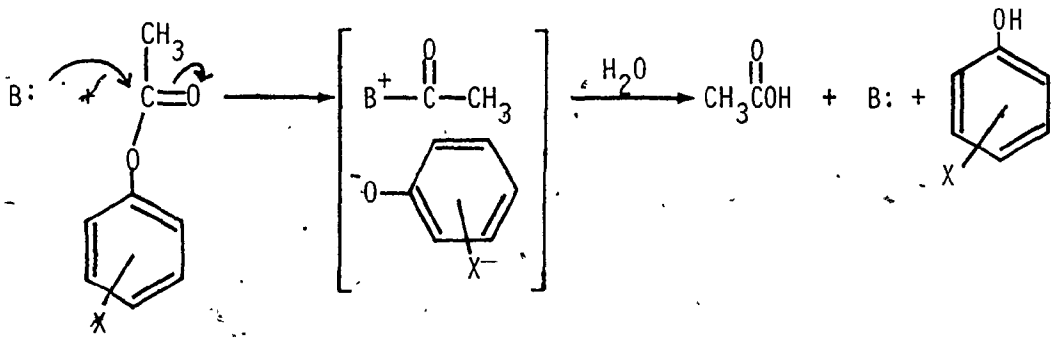
hydrolysis of aryl acetate esters.

SCHEME 1.3

General Base Catalysed Hydrolysis.



Nucleophilic Catalysed Hydrolysis



At the present time there is ample evidence in the literature for both general base and nucleophilic catalysed reactions of many types of substrates, although mostly with carbonyl derivatives (20,21).

Both general base and nucleophilic catalysed reactions will furnish a conventional Brönsted plot (log k_B versus pK_a) if the Brönsted equation is obeyed by the reaction being studied. General base and nucleophilic catalysed reactions are kinetically indistinguishable in form (21), so that some other means must be employed in order to distinguish between these mechanisms. The magnitude of the Brönsted coefficient (β) is not

usually helpful in distinguishing between the two means of catalysis. Although β values >1 may suggest nucleophilic catalysis (22), the majority of β values for general base and nucleophilic catalysis are in the range 0.2 - 1.0.

As may be seen from Scheme 1.3, general base catalysed hydrolysis involves the removal of a proton from water in the rate determining step, whereas nucleophilic catalysis only involves the catalyst and the substrate. The two most common means of distinguishing between the two catalytic mechanisms has exploited this fundamental difference. The criteria most often employed are: a) the magnitude of the kinetic solvent isotope effect (KSIE), and b) the extent to which any hindered catalysts (in the case of substituted pyridine catalysts this refers to ortho substituted pyridines) fall below the Brönsted line which is established using unhindered catalysts. Generally, mechanisms where general base catalysis is operating show larger KSIE (i.e. $k_{\psi(H_2O)}/k_{\psi(D_2O)} \geq 2$) and smaller absolute deviations from the Brönsted line for the hindered catalysts than for reactions which involve nucleophilic catalysis (21,23). However, the dividing line for distinguishing between the two mechanisms by these criteria is not always very clear.

At the present time there are generally accepted to be three circumstances which are needed for effective nucleophilic catalysis to be operating in a reaction (20):

a) "The catalyst must have a higher nucleophilic reactivity than the final functional group acceptor under the conditions of the experiment.

b) The intermediate which is formed by reaction of the substrate with the catalyst must be more reactive than the substrate.

c) The intermediate must be thermodynamically less stable than the product, so that it does not accumulate instead of the final product."

One pathway which obeys these criteria is illustrated by the energy level diagram shown in Figure 1.1.

A common feature of both general base and nucleophilic catalysed reactions has been the observation that not all classes of unhindered bases are necessarily described by the same Brönsted equation. It is usually the case that each series of structurally similar bases (eg. trialkylamines, substituted pyridines and imidazoles) will define separate Brönsted equations which are based upon their ability to catalyse a particular reaction (20).

An example of a tertiary amine catalysed reaction of a sulfonyl chloride is the pyridine catalysed hydrolysis of aromatic sulfonyl chlorides, a reaction which has been investigated by Rogne (24,25). Rogne found that the reaction product was the aromatic sulfonic acid, yet the kinetic rate law for the reaction was first order in both sulfonyl chloride and substituted pyridine. This indicated that a base catalysed hydrolysis reaction was indeed operating here. From the very low KSIE ($k_{\psi(H_2O)}/k_{\psi(D_2O)}$ = 1.10) he proposed that the reaction mechanism was nucleophilic catalysis, proceeding via a sulfonylpyridinium ion intermediate (Scheme 1.4). There were no hindered pyridines employed in this study, but for the analogous reactions performed in methanol, 2-picoline was observed to be ≥100 times slower than an unhindered base of identical basicity.

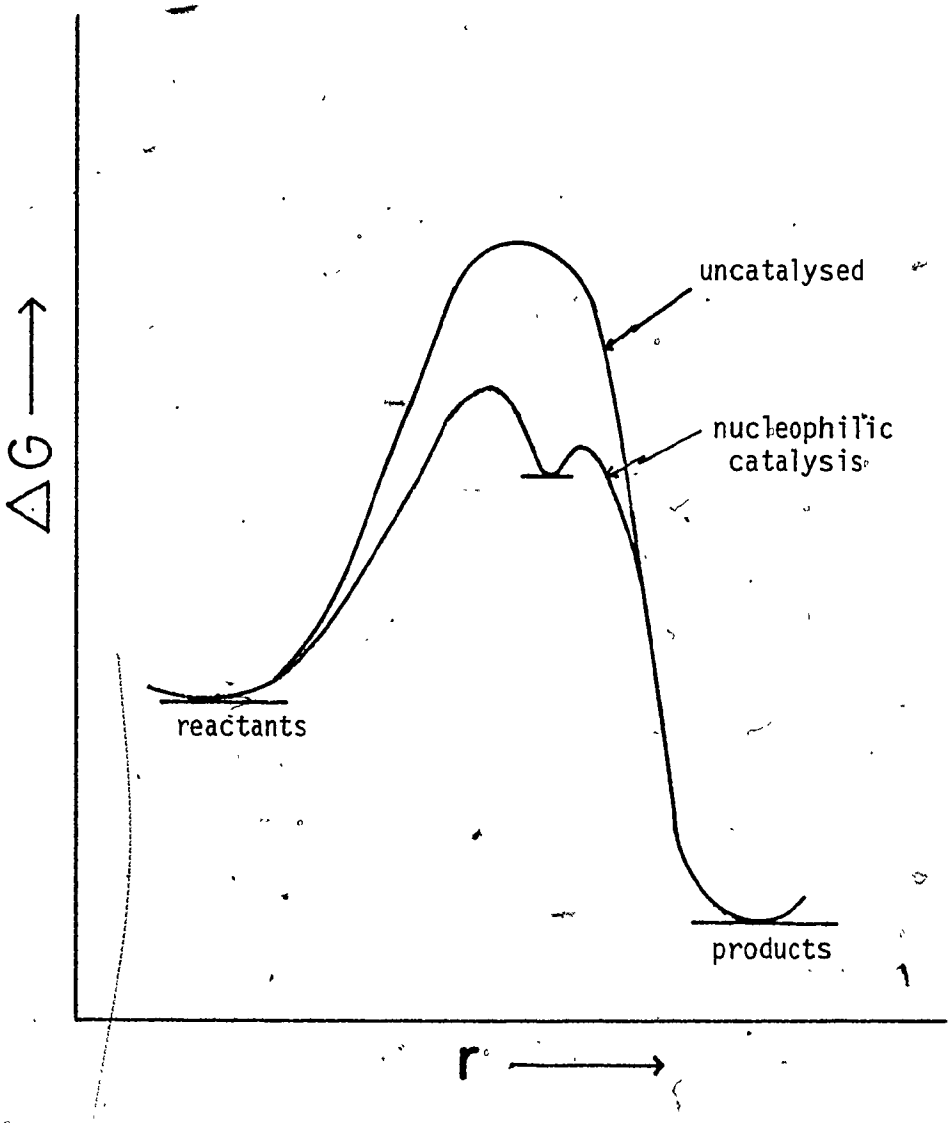
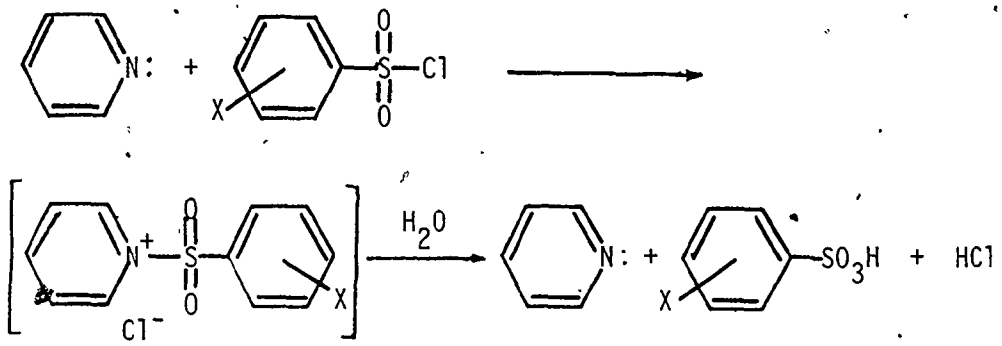


FIGURE 1.1

Nucleophilic Catalysis

SCHEME 1.4

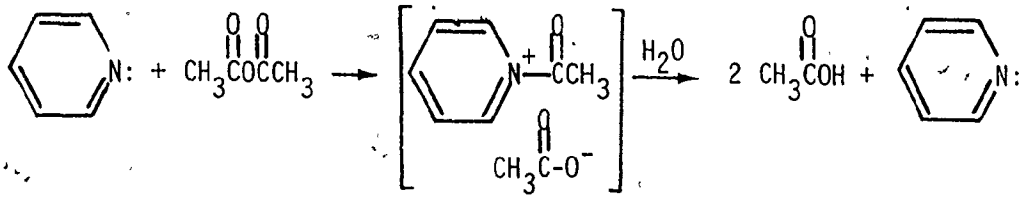


X = p-CH_3O, p-CH_3, H, m-NO_2, p-NO_2

Through subsequent work Rogne was able to extend the nucleophilic catalysed hydrolyses of substituted benzenesulfonyl chlorides to include catalysis by such nucleophiles as acetate and nitrite ion (26).

The nucleophilic catalysed hydrolyses of benzenesulfonyl chlorides was similar in nature to the hydrolysis of acetic anhydride which was also found to be catalysed by substituted pyridines (27,28). This reaction which is, of course, a common synthetic method for acetylating alcohols, was investigated by Gold and co-workers in the late 1950's. The reaction was established to proceed via the acetylpyridinium ion (4) intermediate, as shown in Scheme 1.5.

SCHEME 1.5



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Shortly after Rogne's investigation of the pyridine catalysed hydrolysis of substituted benzenesulfonyl chlorides in water, Ciuffarin (29) extended this study into a series of water-acetonitrile solvent mixtures. The effects of solvent composition upon the rates of the hydrolysis reactions (and the resulting Brönsted β coefficients) of benzenesulfonyl chloride with unhindered pyridines and anilines was determined. Ciuffarin observed that the second order rate constants passed through a maximum at a mole fraction of water (X_{H_2O}) of 0.9, and that the Brönsted coefficients steadily increased as X_{H_2O} decreased from 1.000 to 0.202. The data for the reactions with pyridines at 0° are shown in Table 1.1.

TABLE 1.1

Brönsted β Values for Reactions of Benzenesulfonyl Chloride with Substituted Pyridines in Aqueous Acetonitrile Mixtures at 0°C

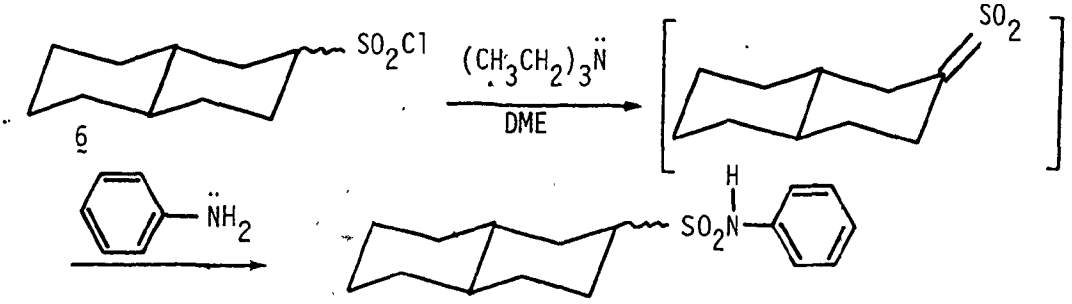
X_{H_2O}	β
1.000	0.43
0.953	0.49
0.693	0.63
0.202	0.79

The Brönsted plots (log k_B versus pK_a) were determined using only three substituted pyridine bases however, so that the reported β values undoubtedly have a considerable error associated with them. Nevertheless, this study marked the first instance where Brönsted coefficients were found to change as the composition of the solvent was altered, while the overall reaction remained the same. Beyond the qualitative remark that

the value of β was larger in the relatively less polar solvent compared with pure water, the authors declined to speculate upon the further significance of their results.

For the reactions of alkanesulfonyl chlorides with tertiary amines, King and co-workers have clearly shown in several instances that nucleophilic catalysis is an insignificant process. The Brönsted plot constructed for the reactions of methanesulfonyl chloride (5) with 3° amines in 1,2-dimethoxyethane (DME) was found to be linear, and no deviations were observed when hindered amines were employed (30).

King and Lee (31) established that the reaction of axial trans-decalin-2(a)-sulfonyl chloride (6) with triethylamine in DME at -25° proceeded 71 times faster than the equatorial epimer, a result in agreement with direct sulfene formation but not nucleophilic catalysis.



6

For the reaction of methanesulfonyl chloride (5) with tertiary amines in D_2O, King and co-workers have shown (32) that the reaction proceeds exclusively by sulfene formation when trimethylamine, dimethylethylamine, and diethylmethylamine are employed. By extension of these results, triethylamine would also be expected to generate sulfene as an intermediate.

The existence of a general base catalysed alcoholysis reaction for some aliphatic and aromatic sulfonyl chlorides has been proposed when triethylamine is employed as a base (33). It has also been suggested that mechanisms not involving a sulfene intermediate become more

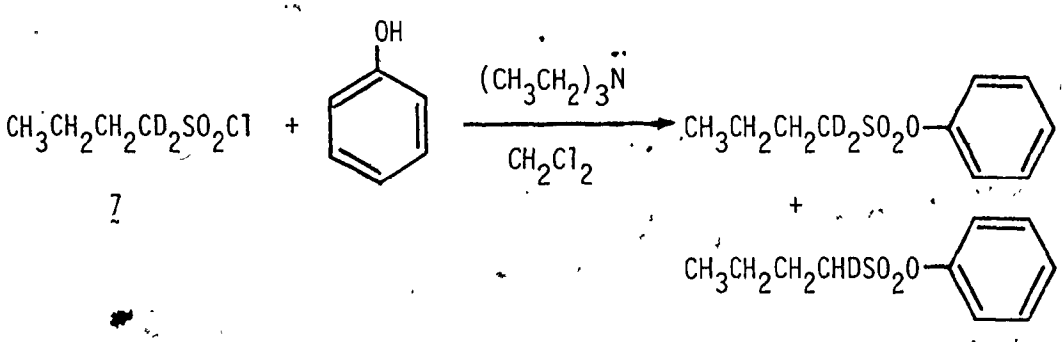
important when tertiary amines of lower basicity are employed in the alcoholyses of alkanesulfonyl chlorides, namely nucleophilic and general base catalysis (33). However, at the present time the conditions under which the general base catalysis mechanism comprises a significant proportion of the total reaction of a sulfonyl chloride to generate a substitution product, have not yet been clearly defined.*

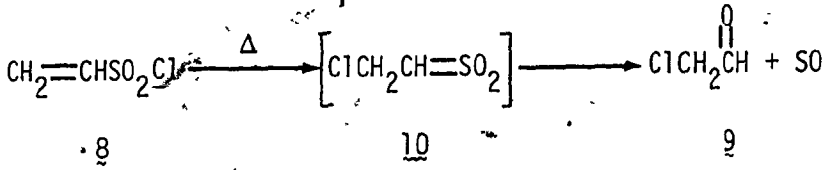
Whereas substantial effort has been directed in the past towards studying the hydrolyses and alcoholyses of aromatic and aliphatic sulfonyl chlorides in the presence and absence of catalysts, relatively few such studies have been performed with alkenesulfonyl chlorides. The recent organic syntheses performed using "[2] betylates" (prepared from ethenesulfonyl chloride (8)) in our laboratory may help stimulate interest in the reactions of alkenesulfonyl chlorides (35).

In the 1960's ethenesulfonyl chloride (8) was shown to undergo flash thermolysis to yield chloroacetaldehyde (9) (25%) and probably sulfur monoxide (36). This reaction was proposed to proceed via a chloromethylsulfene (10) intermediate.

---

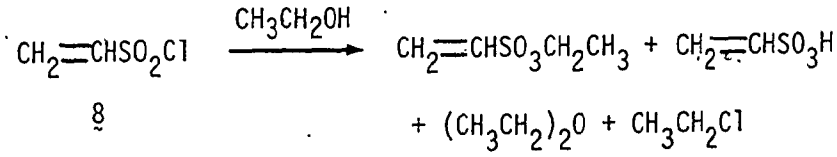
*Unpublished results in our own laboratory have suggested that a general base catalysed alcoholysis mechanism may be involved to a limited extent in the reaction of α-d_2-1-butanesulfonyl chloride (7) with triethylamine and phenol in methylene chloride, but in much smaller measure with methanol (34).





8 10 9

About this time Scott (37) demonstrated that the ethanolysis of 8 produces the ethenesulfonate ester contaminated with ethenesulfonic acid.



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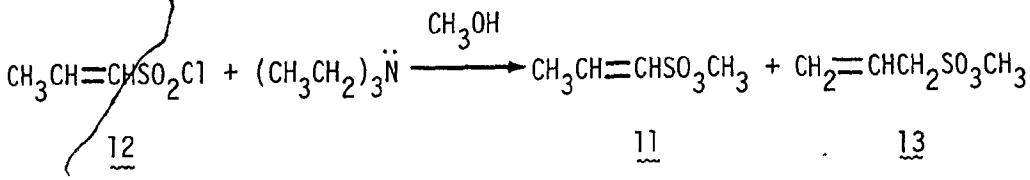
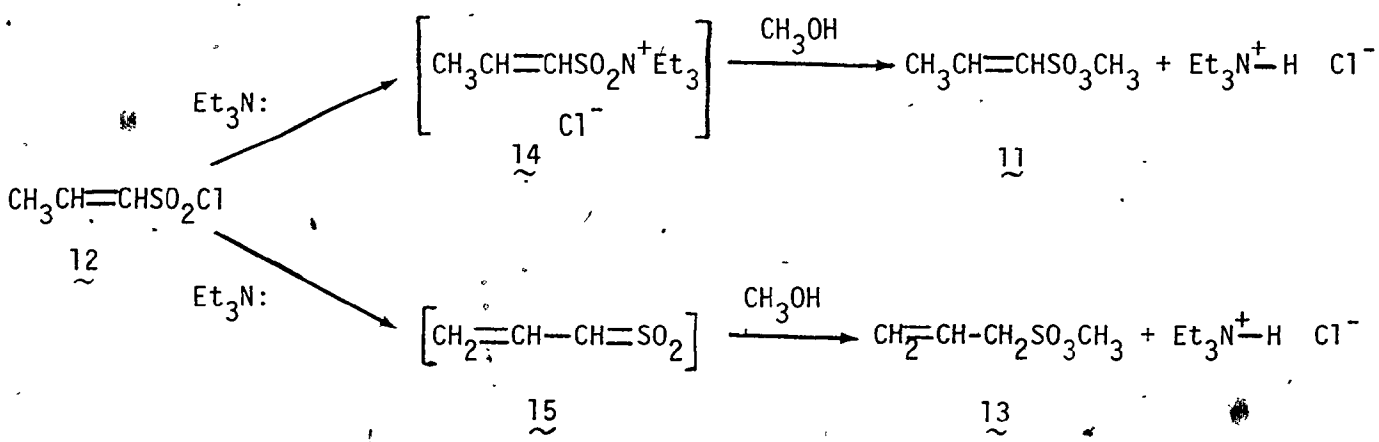
Also in the 1960's, Truce and Campbell (38) investigated the reaction of 1-propene-1-sulfonyl chloride (12) with triethylamine in the presence of methanol. The observed products of this reaction were methyl 1-propene-1-sulfonate (11) and methyl 2-propene-1-sulfonate (13), in 33% and 67% yields respectively.



12 11 13

The authors concluded that these two products were derived by separate mechanisms from 12. The minor product 11 was proposed to have been derived by conventional nucleophilic (S_N2) catalysis at sulfur by triethylamine, followed by methanolysis of the intermediate propene-1-sulfonyl triethylammonium chloride (14). The major product 13 was suggested to have been formed by the 1,2 addition of methanol to a vinylsulfene (15) intermediate (generated by a base promoted elimination reaction of 12), as shown in Scheme 1.6.

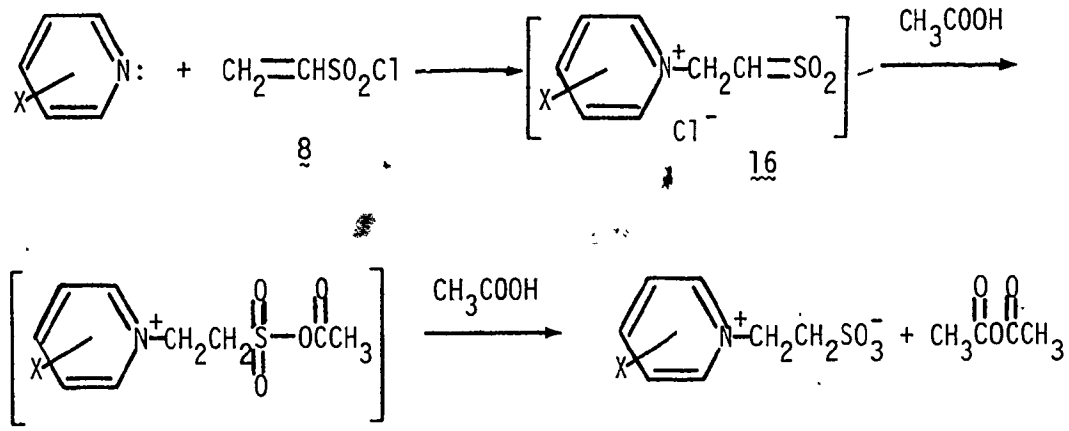
SCHEME 1.6


CH3CH=CHSO2Cl
12
Et3N:
[CH3CH=CHSO2N+Et3 Cl-]
14
CH3OH
CH3CH=CHSO3CH3 + Et3N+-H Cl-
11
Et3N:
[CH2=CH-CH=SO2]
15
CH3OH
CH2=CH-CH2SO3CH3 + Et3N+-H Cl-
13

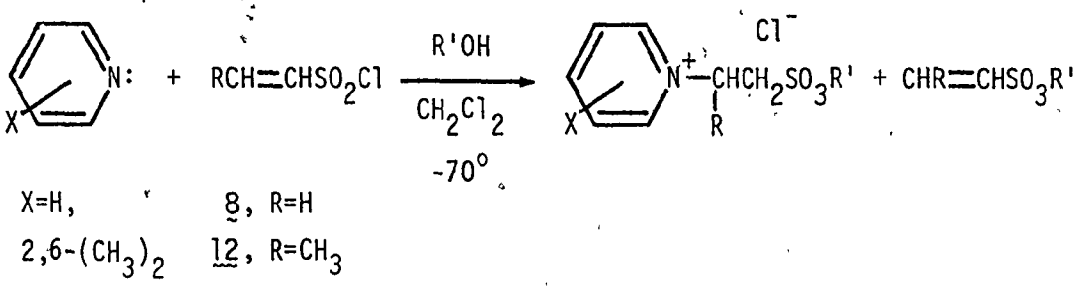
While these separate mechanisms did adequately explain the reaction products (and their deuteration patterns when CD_3OD was employed), no alternative mechanisms were considered nor was any other evidence presented to support the proposed scheme. This reaction apparently marked the first instance where an alkenesulfonyl chloride was treated with a tertiary amine in the presence of a sulfene trapping agent.

In 1970 Le Berre et al (39) reacted ethenesulfonyl chloride (8) with various pyridine bases in acetic acid and obtained excellent yields of pyridine sulfobetaines. They proposed that the reaction was proceeding via a pyridiniosulfene (16) intermediate, as shown in Scheme 1.7.

SCHEME 1.7



Several years ago King and Loosmore (40) investigated the reactions of ethenesulfonyl chloride (8) and 1-propene-1-sulfonyl chloride (12) with tertiary amines in the presence of alcohols at -70° in methylene chloride. The initial study was performed with substituted pyridine bases and isopropyl alcohol. The reaction products were identified as an alkenesulfonate ester and a substituted pyridinioethanesulfonate ester ("[2] betylate") formed in a 2:1 relative proportion.

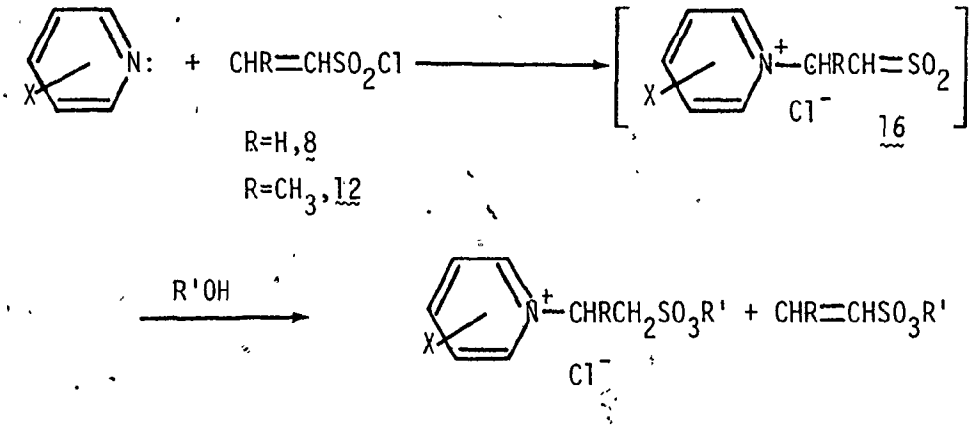


X=H, 8, R=H

2,6-$(CH_3)_2$ 12, R=CH_3

Pyridine was observed to react about 10,000 times faster than 2,6-lutidine with 8 under these reaction conditions. Pyridine also reacted about 500 times faster with 8 than with 12 under the identical reaction conditions. These results along with other available data led them to propose a common intermediate for the production of both sulfonate esters. This proposed intermediate was the pyridiniosulfene (16) intermediate derived by an S_N2' (vinylogous nucleophilic substitution) reaction of the pyridine base on 8 or 12, as illustrated in Scheme 1.8.

SCHEME 1.8

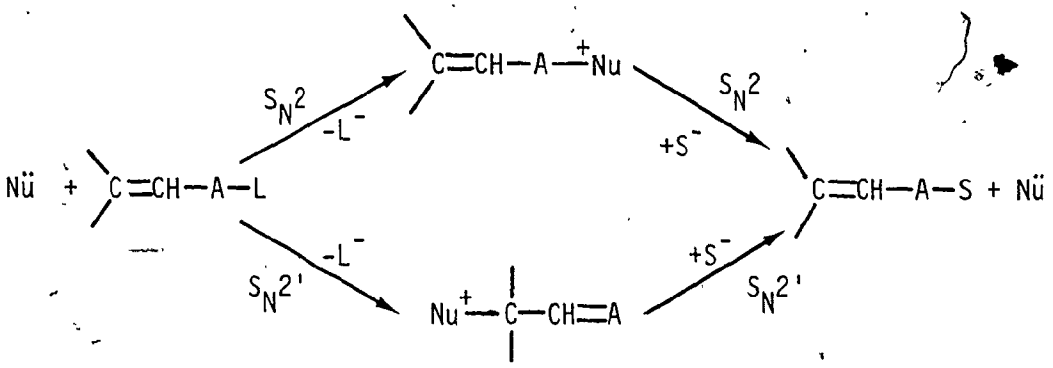


Subsequent trapping of this pyridiniosulfene (16) intermediate with an alcohol was proposed to be responsible for the generation of the ethenesulfonate ester and the [2] betylate. It is evident that the generation of the alkenesulfonate ester from the alkenesulfonyl chloride

by way of the pyridiniosulfene (16) corresponds to a catalytic reaction by the base.

Since bimolecular nucleophilic substitution at a center bearing a 1—alkenyl group may proceed either by direct (S_N2) or vinylogous (S_N2') attack, it is not unexpected that nucleophilic catalysis of displacement at such a center should have the same potential for mechanistic duality (see Scheme 1.9).

SCHEME 1.9



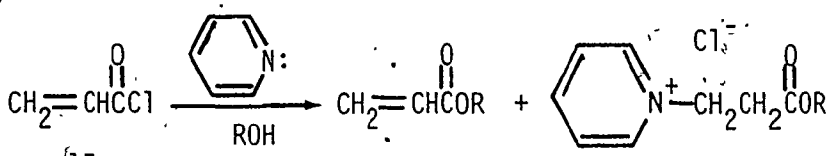
The lower pathway in this Scheme represents vinylogous nucleophilic catalysis by nucleophile Nü. The major difference between the mechanism proposed by King and Loosmore (40) and the work of Le Berre (39) is that for the reactions performed in methylene chloride, the pyridine base functions as a true catalyst (i.e. in the formation of the ethenesulfonate ester).

The double bond of ethenesulfonic acid derivatives has long been known to react with a variety of nucleophiles (41), as illustrated by the easy addition of alcohols, 1^o, 2^o amines to ethenesulfonate esters. If these precedents are considered, it does not seem unreasonable to

$$ROH + CH_2{=}CHSO_3R' \longrightarrow ROCH_2CH_2SO_3R'$$

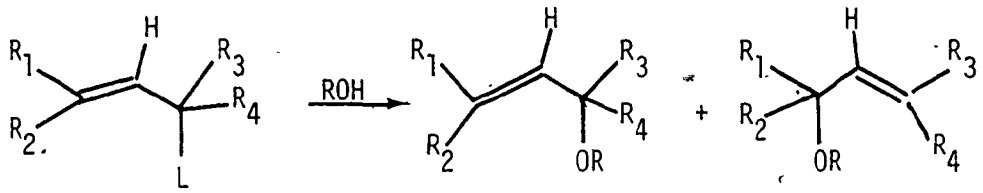
suggest that pyridine could react with ethenesulfonyl chloride (8) in an S_N2' reaction to generate the sulfene (16).

A ketene intermediate analogous to the sulfene (16) has been implicated in the reactions of acryloyl chloride (17) with tertiary amines and alcohols (42), but the mechanism of ketene formation or its possible involvement in S_N2' catalysis reactions had not been explored until very recently.*



17 15% 45%

The traditional S_N2' reaction on an allylic carbon substrate has enjoyed a colorful history. This mechanism was conceived independently by three researchers in the late 1930's as an explanation for the formation of "abnormal" substitution products which were observed when allylic halides were solvolysed (44-47).



L=Cl, Br, I "normal" product "abnormal" product

During the quest for irrefutable evidence for the existence of the S_N2' mechanism, several conditions were proposed to be fulfilled before a product could be said to be derived from an S_N2' reaction (47).

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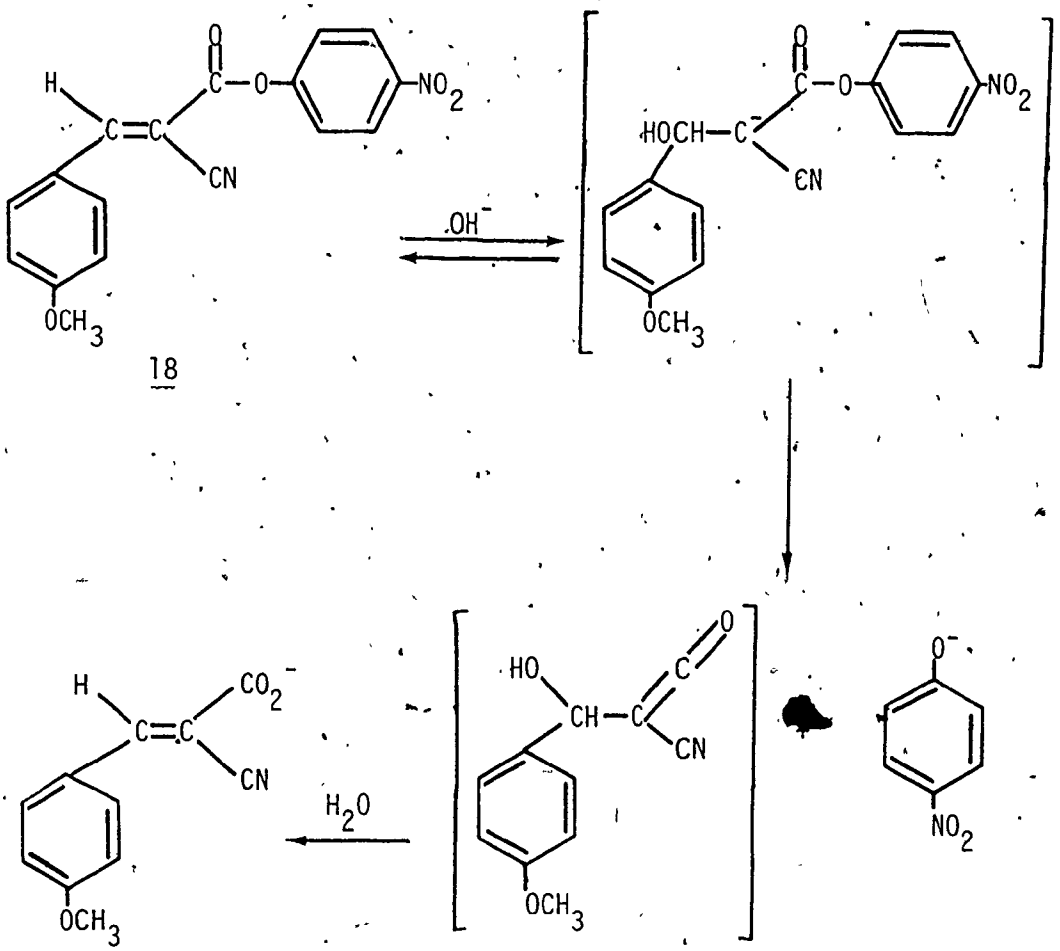
*A similar ketene intermediate has been proposed (43) in the specific base catalysed hydrolysis of p-nitrophenyl-2-cyano-3-(p-methoxyphenyl)-propenoate (18) to generate the corresponding carboxylate anion. (See Scheme 1.10).

SCHEME 1.10



18

a) "The rate of the reaction must be proportional to the concentration of both the substituting reagent and the compound being substituted (usually this implies second order kinetics).

b) The reaction must give isolable amounts of abnormal substitution products.

c) It must be demonstrated that neither the substrate nor the normal substitution product undergoes rearrangement under the conditions of the reaction."

Using these stringent requirements for the evaluation of experimental results, it remained until 1949 for Winstein (48) to establish that an "abnormal" product was indeed formed by an S_N2' reaction of allylic chlorides with sodium diethylmalonate.

$$CH_2{=}CHCHCl \xrightarrow{Na^+\ \bar{C}H(CO_2CH_2CH_3)_2} CH_2{=}CH{-}CHCH(CO_2CH_2CH_3)_2$$

R = CH_3 or CH_2CH_3

"normal" product

+

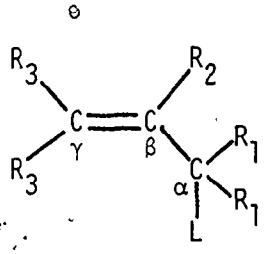
$(CH_3CH_2O_2C)_2CHCH_2CH{=}CHR$

"abnormal" product
10-23%

In the years following this work experimental evidence has been gradually collected in support of the S_N2' reaction, with the bulk of the work having been done with a carbon skeleton.

Since there is apparently a delicate balance between the relative facility of competing S_N2 and S_N2' reactions for some allylic compounds, it would not be unreasonable to expect that slight modifications in substrate structure could alter the reaction from mostly S_N2 to mostly

S_N2' or vice versa. Consequently, a large amount of the subsequent work with allylic substrates has been concerned with determining substituent effects upon the relative ease of the S_N2' reaction. For an allylic skeleton where L is a reasonable leaving group, "normal" (S_N2)

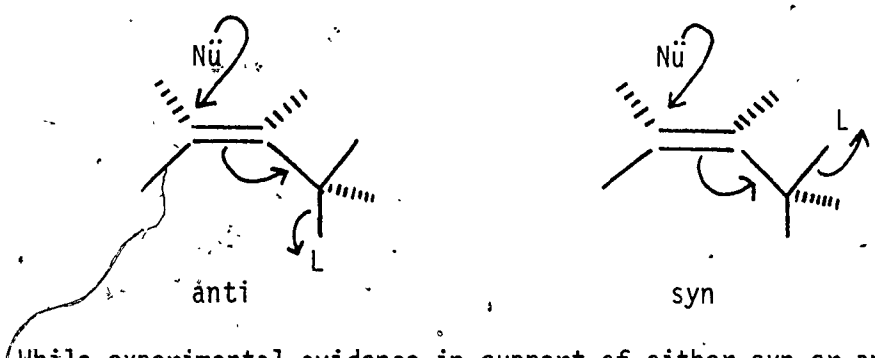


L = Cl, Br, I, OCR (O)

substitution at the α carbon by a nucleophile is retarded by R_1 substituents larger than hydrogen (47). This has been reasonably attributed to a steric effect since it occurs when R_1 is an electron withdrawing or an electron donating group. Substituents at the β carbon of the allylic system should affect the reactivity at adjacent centers largely by an inductive effect, and any rate differences which are attributed to β substituents are usually small. Alkyl, aryl and halogen substituents on the γ carbon have been shown to increase the rate of the S_N2 reaction relative to the S_N2' reaction. It would not be unreasonable to expect that bulky substituents on the γ carbon might slow the rate of the S_N2' reaction due to steric hindrance to nucleophilic attack at this position. On the other hand extensive alkyl substitution on the α carbon, while precluding the S_N2 reaction, may actually facilitate an S_N1 solvolysis reaction to generate some abnormal reaction products. In such a situation the isolated abnormal reaction products may be due to a combination of the S_N2' and S_N1 reactions of the substrate.

The stereochemistry of the S_N2' reaction has also been the subject of a substantial amount of research in the past (49). In theory the

the entering nucleophile (Nü) and the leaving group (L) may react on the same face of the allylic system (designated as syn attack), or may react on opposite sides of the double bond (anti attack). However, a common feature of both mechanisms is the preference for the periplanar arrangement of Nü and L in order to achieve maximum orbital overlap (50) with the π system.



While experimental evidence in support of either syn or anti attack is meager and often contradictory (49), the bulk of the experimental studies to date have indicated at least a preference for syn attack for most allylic substrates. Consequently the stereochemistry of the S_N2' reaction is usually described as stereoselective (49).

The initial results of King and Loosmore (40) with ethenesulfonyl chloride (8) and 1-propene-1-sulfonyl chloride (12) pointed towards a third mechanism of substitution at sulfonyl sulfur for α, β unsaturated sulfonyl chlorides. The work presented in this thesis describes the continuing study of the reactions of 8 and 12 with a wide range of substituted pyridines. This study was performed in a purely aqueous medium and in aqueous mixtures of 1,2-dimethoxyethane (DME), in contrast to the study performed by King and Loosmore. This medium was chosen because of the potential ease of determining the rates of hydrolysis by the well-established pH-stat technique (51), and also because the products of these reactions in water were expected to be stable under the

reaction conditions. "[2]Betylates" had been shown to react rapidly with even feeble nucleophiles under mild reaction conditions (40) to generate alkylation products, and these complications could be removed by performing the reactions in water.

1.2 Results and Discussion

(a) The Hydrolysis of Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12) in Water Containing 0.1 M Potassium Chloride at 25.0°C

The rates of the hydrolysis of ethenesulfonyl chloride (8) and trans-1-propene-1-sulfonyl chloride (12) were determined at 25.0° in 0.1 M potassium chloride solution at several different pH values using the pH stat technique. The pseudo first order rate constants (k_ψ)* for these hydrolyses were obtained from the slopes of the lines generated from plots of log (V_∞-V_t) versus time.‡

These plots were straight to ≥90% reaction (unless otherwise noted), indicating that the hydrolysis reactions were first order in the sulfonyl chloride. The results are given in Tables 1.2 and 1.3. From these data it was possible to construct pH-rate profiles (log k_ψ versus pH) for the hydrolysis reaction of each sulfonyl chloride at 25.0°. These pH-rate profiles are illustrated in Figures 1.2, 1.3. Both of these plots are quite similar in shape, each displaying both a flat region in the neutral and acidic pH region as well as a rapidly increasing rate at higher pH values. The behavior of the two unsaturated sulfonyl chlorides 8 and 12 was consistent with the following rate law:

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*A complete listing of all the symbols used in this discussion to denote empirical and mechanistic rate constants is given in Appendix 1.

‡V_∞ = end point titre (mL) at infinite time (usually recorded at ≥10 half lives).

V_t = titre (mL) at time t.

TABLE 1.2

Observed Pseudo-First Order Rate Constants for the Hydrolysis of Ethenesulfonyl Chloride (8) in 0.1 M Potassium Chloride at 25.0°C

initial sulfonyl chloride concentration: 1×10^{-3} M

pH	$10^3 \cdot k_\psi (s^{-1})$	$-\log k_\psi$
2.0	1.32	2.88
3.0	1.22	2.91
4.0	1.27	2.90
5.0	1.30	2.89
6.0	1.40	2.85
7.0	1.38	2.86
8.0	1.38	2.86
9.0	2.65	2.58
9.6	5.83	2.23
10.0	14.3	1.84
10.5	45.5	1.34
10.75	64.9	1.19
10.75	67.1	1.17

TABLE 1.3

Observed Pseudo First Order Rate Constants for the Hydrolysis of trans-1-Propene-1-sulfonyl Chloride (12) in 0.1 M Potassium Chloride at 25.0°C

initial sulfonyl chloride concentration: 1×10^{-3} M

pH	$10^3 \cdot k_\psi (s^{-1})$	$-\log k_\psi$
3.0	1.18	2.93
4.0	1.19	2.92
5.0	1.13	2.95
6.0	1.28	2.89
7.0	1.21	2.92
8.0	1.34	2.87
9.0	1.59	2.80
9.5	2.50	2.60
10.0	5.33	2.27
10.5	12.3	1.91
10.8	23.4	1.63
11.0	33.5	1.47

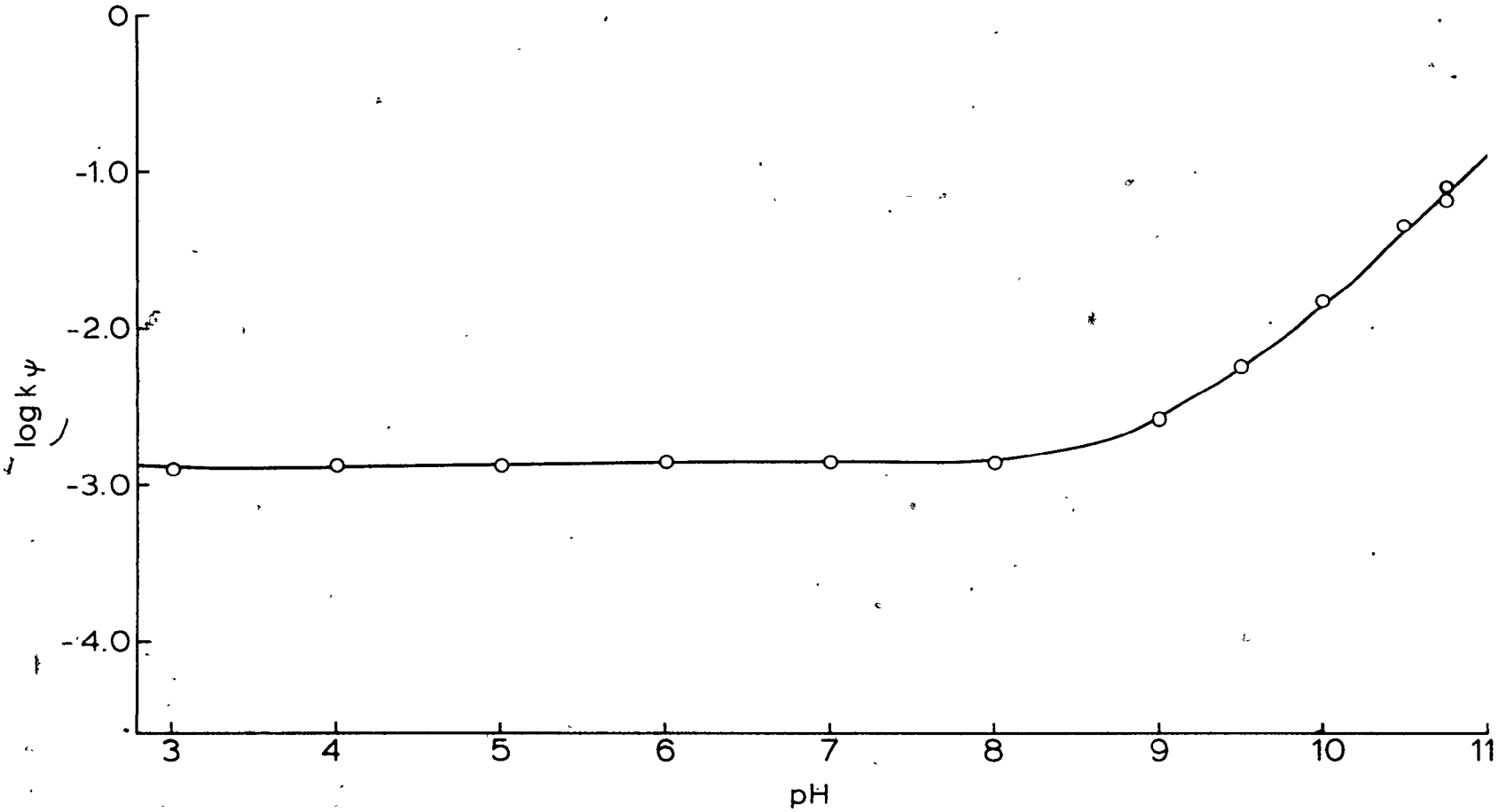

FIGURE 1.2 pH-Rate Profile for Ethenesulfonyl Chloride (8) in Water at 25.0°C

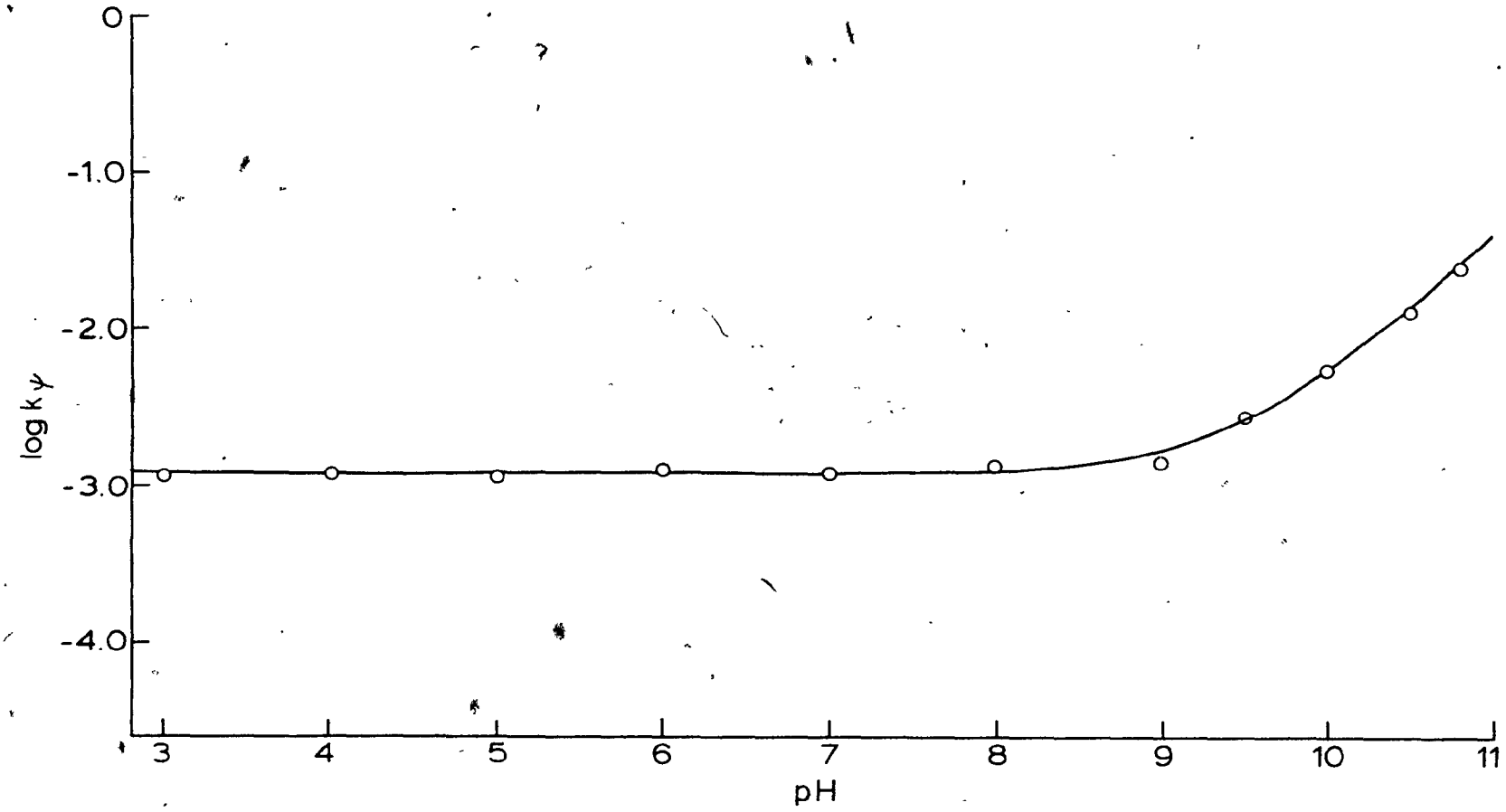

FIGURE 1.3 pH-Rate Profile for trans-1-Propene-1-sulfonyl Chloride (12) in Water at 25.0°C

$$-\frac{d[S]}{dt} = k_{\psi}[S]$$

where $k_{\psi} = k_1 + k_{OH^-}[OH^-]$

and $[S]$ = concentration of the sulfonyl chloride

Using this rate law for each sulfonyl chloride, it is possible to determine mean values of k_1 and k_{OH^-} from the observed rate constants (k_{ψ}'s) obtained at various pH values. A mean value of k_1 was calculated from the observed k_{ψ}'s in the pH region 2-8. From the observed k_{ψ}'s at pH values $\geq$9.0 and the mean value of k_1, individual values of k_{OH^-} were calculated for reaction at each pH. The mean of these k_{OH^-} values was then calculated. These data are given in Table 1.4.

mean k_1 for 8 = $1.32 \pm 0.07^* \times 10^{-3}$ s^{-1}

mean k_1 for 12 = $1.22 \pm 0.08^* \times 10^{-3}$ s^{-1}

The curves displayed for the pH-rate profiles were constructed using the mean values of k_1 and k_{OH^-} in conjunction with the rate law presented above.

The products of these hydrolyses were also determined at several different pH values at 25.0° for both unsaturated sulfonyl chlorides, using varying initial concentrations of the sulfonyl chloride. After these reactions were judged to be complete (usually indicated by no further addition of titrant solution)** the solvent was evaporated and the residue was investigated by ^1H n.m.r. spectroscopy. For all of the

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*Standard deviation

**The end point titres of the kinetic runs and the product determination experiments agreed with the theoretical values calculated on the basis of the observed reaction products.

TABLE 1.4

Rate Constants for Reaction of Hydroxide Ion with Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12) in 0.1 M Potassium Chloride at 25.0°C

Ethenesulfonyl Chloride (8)

initial sulfonyl chloride concentration: 1×10^{-3} M

pH	$10^5 \cdot [OH^-]$ (M)	$10^3 \cdot k_\psi$ (s^{-1})	k_{OH^-} ($M^{-1}s^{-1}$)
9.0	1.0	2.65	133
9.6	4.0	5.83	113
10.0	10	14.3	130
10.5	32	45.5	140
10.75	56	64.9	113
10.75	56	67.1	117

mean $k_{OH^-} = 124 \pm 11^{(a)}$ $M^{-1}s^{-1}$

trans-1-Propene-1-sulfonyl Chloride (12)

initial sulfonyl chloride concentration: 1×10^{-3} M

pH	$10^5 \cdot [OH^-]$ (M)	$10^3 \cdot k_\psi$ (s^{-1})	k_{OH^-} ($M^{-1}s^{-1}$)
9.5	3.2	2.50	41
10.0	10	5.33	41
10.5	32	12.3	35
10.8	63	23.4	35
11.0	100	33.5	32

mean $k_{OH^-} = 37 \pm 4^{(a)}$ $M^{-1}s^{-1}$

(a) standard deviation.

hydrolysis reactions of ethenesulfonyl chloride (8) the reaction products contained the expected product, ethenesulfonate anion (19) as well as a small amount of a completely unexpected product, 2-hydroxyethanesulfonate (isethionate) anion (20).

$$\underset{8}{CH_2{=}CHSO_2Cl} \xrightarrow{H_2O} \underset{19}{CH_2{=}CHSO_3^-} + \underset{20}{HOCH_2CH_2SO_3^-}$$

The identity of the ethenesulfonate anion (19) was confirmed by the preparation of its S-benzylthiuronium salt. The isethionate anion (20) was identified by comparison of its ^1H n.m.r. spectrum with that of an authentic specimen.

The hydrolysis products of trans-1-propene-1-sulfonyl chloride (12) were similarly observed to be the expected 1-propene-1-sulfonate anion (21) at all pH values, along with some of the 2-hydroxy-1-propanesulfonate anion (22) product at high pH. These products were identified by their ^1H n.m.r. spectra. The relative proportions of the hydrolysis products at various pH values are given in Table 1.5.

$$\underset{12}{CH_3CH{=}CHSO_2Cl} \xrightarrow{H_2O} \underset{21}{CH_3CH{=}CHSO_3^-} + \underset{22}{CH_3CHOHCH_2SO_3^-}$$

Control experiments confirmed the stability of the reaction products under the conditions of the solvolysis reactions.

(b) Hydrolysis of Ethenesulfonyl Chloride (8) in 0.1 M Potassium Chloride at Several Temperatures

The rates of hydrolysis of ethenesulfonyl chloride (8) at pH 3.0 and several temperatures were determined. The observed pseudo first

TABLE 1.5

Relative Proportions of the Products for the Hydrolysis of the Alkenesulfonyl Chlorides in Water at 25.0°C

Ethenesulfonyl Chloride (8)

pH	[KCl] M	10^2 [S]$_0$ M[a]	Relative Proportions of Products $HOCH_2CH_2SO_3^-$ (20)	$CH_2{=}CHSO_3^-$ (19)
4.0	0	0.16	10%	90%
4.0	0.1	0.16	10	90
4.0	0.1	0.29	12	88
4.0	0.5	0.24	10	90
10.5	0.1	2.9	15	85
10.8	0.1	2.9	13	87

trans-1-Propene-1-sulfonyl Chloride (12)

pH	[KCl] M	10^2 [S]$_0$ M	Relative Proportions of Products $HOCHCH_3CH_2SO_3^-$ (22)	$CH_3CH{=}CHSO_3^-$ (21)
4.0	0.1	2.0	< 2% (b)	> 95%
11.5	0.1	2.0	5	95
12.7	0.1	2.0	5	95

(a) initial concentration of the sulfonyl chloride.

(b) i.e. no sign of any $CH_3CHOHCH_2SO_3^-$ in the ^1H n.m.r. spectrum of the reaction products.

order rate constants (k_ψ) obtained at these temperatures are given in Table 1.6. Using these data an Eyring plot of $\ln(k_{H_2O}/T)$ versus $1/T$ was constructed. It is shown in Figure 1.4. From the slope of the line generated from this plot the activation enthalpy ($\Delta H^\ddagger$) and entropy ($\Delta S^\ddagger$) were calculated* to be 18.0 ± 1.0 kcal mol^{-1} and -20 ± 3 cal deg^{-1} mol^{-1}, respectively.

The errors which are associated with these parameters are the maximum errors as calculated by the method of Wiberg (53). Comparison of these activation parameters with those obtained for the uncatalysed hydrolysis reactions of some aromatic and aliphatic sulfonyl chlorides (Table 1.7) reveals the similarities.

The similarity of these data, along with the isolation of the ethenesulfonate anion (19) as the major (as well as the expected) hydrolysis product is regarded as being consistent with a common hydrolysis mechanism, namely the direct S_N2 attack by water at sulfonyl sulfur.

The small amount of observed isethionate (20) product in these hydrolyses could have been generated by several routes. As is discussed in greater detail in Chapter 4, the results of the hydrolyses of 2-hydroxyethanesulfonyl chloride (23) under varying conditions show that the isethionate (20) product observed in the hydrolysis reaction of 8 cannot have been derived from 23. These experiments also show that no

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*From (52); $k_\psi = \left(\frac{\kappa T}{h}\right) e^{\Delta S^\ddagger/R} \quad e^{-\Delta H^\ddagger/RT}$.

where h = Planck's constant; κ = Boltzmann's constant;
R = gas constant; T = temperature (K)

$$\therefore \ln\left(\frac{k_\psi}{T}\right) = \ln\left(\frac{\kappa}{h}\right) + \frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{RT}$$

TABLE 1.6

Observed Pseudo First Order Rate Constants for the Hydrolysis of Ethenesulfonyl Chloride (8) in 0.1 M Potassium Chloride at pH 3.0 and Several Temperatures

Temp.(°C)	$10^3 \cdot k_\psi (s^{-1})$	$10^5 \cdot k_{H_2O} (s^{-1})$ [a]	$10^3 \cdot 1/T (K^{-1})$	$-\ln(k_{H_2O}/T)$
17.2	0.514	0.926	3.44	17.3
25.0	1.22	2.20	3.35	16.4
35.0	2.91	5.24	3.25	15.6
45.0	7.18	12.9	3.14	14.7
60.0	34.7	62.5	3.00	13.2

(a) $k_{H_2O} = k_1/[H_2O]$ where $[H_2O] \simeq 55.5$ M.

note: under the conditions of these experiments $k_1 = k_\psi$.

TABLE 1.7

Activation Parameters for the Uncatalysed Hydrolysis Reactions of Some Sulfonyl Chlorides

Sulfonyl Chloride	$\Delta H^\ddagger$ (Kcal mol^{-1})	$\Delta S^\ddagger$ (cal deg^{-1} mol^{-1})
$C_6H_5SO_2Cl$ [a,c]	16.4 ± 0.2	-23.1 ± 0.8
$4\text{-}NO_2C_6H_4SO_2Cl$ [a,c]	16.6 ± 0.3	-22.3 ± 0.9
$4\text{-}CH_3OC_6H_4SO_2Cl$ [a,c]	15.2 ± 0.3	-26.0 ± 0.1
CH_3SO_2Cl [b]	20.0 ± 0.7	-8.9 (-17.0 [c])
$CH_3CH_2SO_2Cl$ [b]	18.8 ± 0.2	-11.5 (-22.0 [c])
$CH_2{=}CHSO_2Cl$ [c,d]	18.0 ± 1.0	-20 ± 3

a) From Rogne (17), in 0.05 M potassium chloride.
b) From Hambly (8), in aqueous dioxane ($X_{H_2O} = 0.99$).
c) calculated from the Eyring equation using $k_{H_2O} = k_\psi/[H_2O]$.
d) present work.

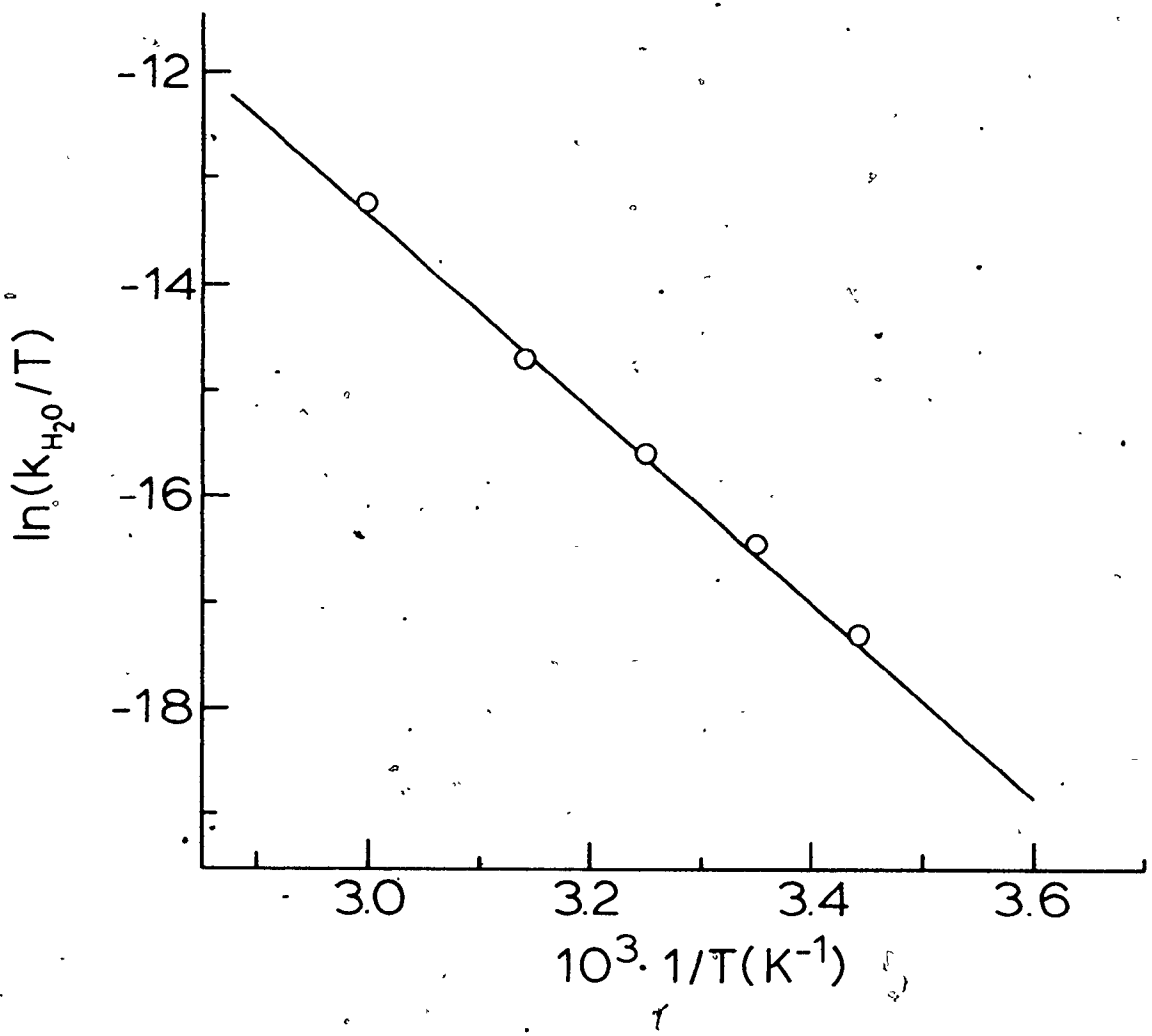


FIGURE 1.4 Eyring Plot for the Uncatalysed Hydrolysis of Ethenesulfonyl Chloride (8) in Water

$$CH_2{=}CHSO_2Cl \xrightarrow{H_2O} \left[HOCH_2CH_2SO_2Cl\right] \xrightarrow{2\,H_2O} HOCH_2CH_2SO_3^- + H_3^+O$$

8 23 20

significant amount of 19 could have arisen via 23. However, a reactive 2-hydroxymethylsulfene (24) intermediate (generated by S_N2' attack of water upon 8) would appear to be both a reasonable and likely precursor of the unexpected hydrolysis product, 20, but not 19 (see Chapter 4).

$$CH_2{=}CHSO_2Cl \xrightarrow{H_2O} \left[HOCH_2CH{=}SO_2\right] \xrightarrow{2\,H_2O} HOCH_2CH_2SO_3^- + H_3^+O$$

8 24 20

The somewhat smaller relative proportion of the 2-hydroxyalkanesulfonate anion derived from 12 versus 8 is also in agreement with this mechanism, since it is to be expected that addition to the double bond would be slowed by the methyl group.

This sulfene (24) intermediate has not specifically been previously proposed, although substantial evidence has been accumulated (5) for the intermediacy of other sulfene intermediates. Chapter 4 presents further evidence for the intermediacy of 24 in the reactions of 23 with tertiary amines in water and methylene chloride. As will be discussed in Chapter 4, the sulfene (24) is probably responsible for the generation of isethionate (20) but not ethenesulfonate anion (19) in the hydrolysis reactions of ethenesulfonyl chloride (8).

(c) The Solvolysis of Ethenesulfonyl Chloride (8) in Deuterium Oxide Containing 0.1 M Potassium Chloride at 25.0° C

The pseudo first-order rate constants for the solvolysis of ethenesulfonyl chloride (8) in D_2O at 25.0° at two different apparent

pH values were determined using the pH-stat technique. The rate constants were observed to be 8.48×10^{-4} s^{-1} at apparent pH 3.4, and 8.68×10^{-4} s^{-1} at apparent pH 5.0 (mean $k_1 = 8.6 \times 10^{-4} \pm 0.1$ s^{-1}). This mean value leads to a kinetic solvent isotope effect (KSIE, $k_1(H_2O)/k_1(D_2O)$) for the uncatalysed hydrolysis reaction of 8 of 1.54 at 25.0°. This KSIE value compares favorably with those obtained by Robertson (54) for methanesulfonyl chloride (6) (1.58 at 20°) and benzenesulfonyl chloride (1.58 at 10°).

The products of the uncatalysed solvolysis of 8 in D_2O at apparent pH 3.4 (using the same initial concentration of 8 as in the kinetic runs) were determined by ^1H n.m.r. spectroscopy. The same products were obtained in roughly the same relative proportion as the reaction performed in water. The isethionate (20) product was observed to be substantially (though perhaps not completely) monodeuterated at the α carbon, and the ethenesulfonate anion (19) was observed to be <5%‡ monodeuterated at the α vinyl carbon.* The observed deuteration pattern in isethionate anion (20) is consistent with the formation of the hydroxymethylsulfene (24) intermediate.

The evidence available so far suggests that the majority of the hydrolysis reaction of 8 proceeds by direct S_N2 attack at sulfur (represented by k_D in Scheme 1.11) to generate 19, and that approximately 10% proceeds by S_N2' attack at carbon (represented by k_C) to

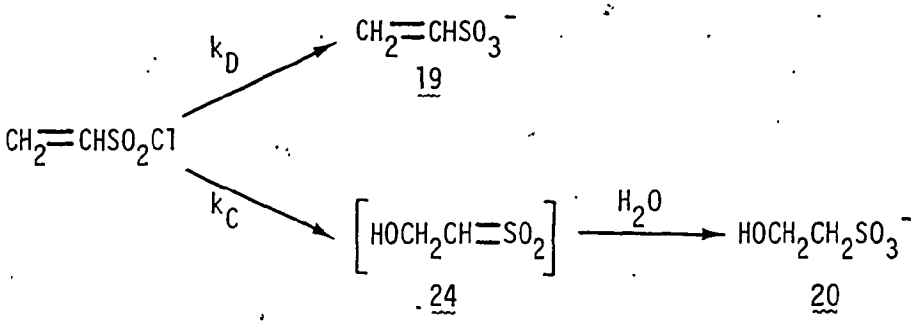
---

‡No peaks ascribable to α monodeuterated 19 were observed in the ^1H n.m.r. spectrum; the chemical shifts of the β vinyl protons of undeuterated and α deuterated 19 were sufficiently different to allow quantitative measurements of the extent of deuteration of 19 by n.m.r. integration.

*Several preliminary experiments performed using larger initial sulfonyl chloride concentrations ($\geq 2 \times 10^{-3}$ M) resulted in the observation of significant and highly variable amounts of monodeuterated 19. The reasons for this behavior are unclear at this time.

generate 24, and then isethionate (20).

SCHEME 1.11



Therefore the overall rate constant k_1 is actually a composite of k_C and k_D, such that $k_1 = k_C + k_D$. If we compare the mean k_D's for 8 ($k_D = 1.19 \pm 0.07 \times 10^{-3}\ s^{-1}$)* and 12 ($k_D = 1.22 \pm 0.08 \times 10^{-3}\ s^{-1}$) it is evident that they are identical. This result is not surprising since, for the direct (S_N2) attack of water at sulfonyl sulfur, a beta (β) methyl substituent on an alkenesulfonyl chloride should have only a small effect upon the hydrolysis rate. An alpha (α) methyl group on these alkenesulfonyl chlorides might be expected to have a more pronounced effect upon the rate of hydrolysis, since the substituent would now be closer to the reaction site. The effect of an alpha methyl substituent upon the rate of hydrolysis of alkanesulfonyl chlorides has been found to be significant: dodecane-1-sulfonyl chloride hydrolyses 10 times faster than dodecane-2-sulfonyl chloride at 25.0° in 20% aqueous dioxane (55).

The hydrolysis rates for 8 and 12 are comparable to benzenesulfonyl chloride ($k_\psi = 3.06 \times 10^{-3}\ s^{-1}$ at 25.0° in 0.1 M KCl (9)), but

*Obtained by subtracting 10% of mean k_1 for 8 from k_1.

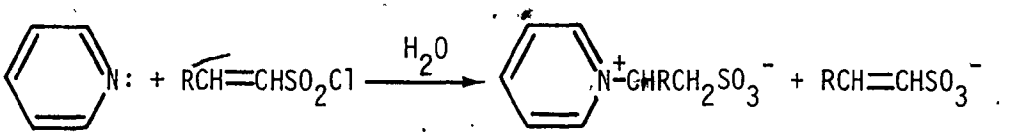
significantly faster than methanesulfonyl chloride (k_ψ = 1.94 × 10^{-4} s^{-1} at 30.0° in water (56). These data are qualitatively in agreement with the increased reactivity of allyl and benzyl substrates compared with alkyl substrates in S_N2 reactions (1,50).

The mean values of k_{OH^-} for 8 and 12 are observed to be significantly different from each other ($k_{OH^-}(8)/k_{OH^-}(12)$ = 3.3). This ratio is in good agreement with that found for the reactions of benzenesulfonyl chloride and p-toluenesulfonyl chloride ($k_{OH^-}(PhSO_2Cl)/k_{OH^-}(p\text{-}CH_3C_6H_4SO_2Cl)$ = 2.5 (17), while their uncatalysed solvolysis rates were identical). The relative reactivity exhibited here is in agreement with an anionic transition state for S_N2 attack at sulfur by hydroxide ion, with stabilization by electron withdrawing groups (17).

(d). Reactions of Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12) with Pyridine in Water and Deuterium Oxide Containing 0.1 M Potassium Chloride at 25.0°C

The reactions of pyridine with 8 and 12 in 0.1 M potassium chloride were studied using the pH-stat technique as described earlier. For the reaction of pyridine with ethenesulfonyl chloride (8), N-pyridinium-2-ethanesulfonate (pyridine betaine) (25a) was isolated by the use of a deionizing resin. The m.p. and mixed m.p. with an authentic specimen of 25a were identical. Ethenesulfonate anion (19) was identified by its characteristic ^1H n.m.r. spectrum. For the reaction of pyridine with 12, the betaine (26a) and 1-propene-1-sulfonate anion (21) were identified by comparison with ^1H n.m.r. spectra of authentic specimens. These reactions are summarized in Scheme 1.12.

SCHEME 1.12



R = H, 8; R = CH_3, 12 — R = H, 25a; R = CH_3, 26a — R = H, 19; R = CH_3, 21

No signals attributable to either isethionate anion (20) or 2-hydroxypropane-1-sulfonate anion (22) were observed in the ^1H n.m.r. spectra of the reaction products. The stability of the products was established by several control experiments performed under the conditions of the product determinations. The results of the product determination experiments are shown in Table 1.8. The nature of the reaction products, as well as their relative proportions were observed to be relatively insensitive to substantial changes in the initial concentration of the reagents employed, provided that the rate of the reaction with 8 was distinctly faster than the rate of the uncatalysed hydrolysis reaction. These results also demonstrated that the relative proportion of the betaine (25a) was independent of the concentration of pyridinium chloride present. This indicated that the product ratio was not influenced by the presence of a general acid.

When the reaction of 8 with pyridine was performed in D_2O at apparent pH 3.4 and 25.0°, the betaine (25a) was formed in 70% relative yield and was estimated (by ^1H n.m.r. integration) to be ≥90% monodeuterated at the alpha (α) carbon. Undeuterated ethenesulfonate anion (19) comprised the remainder of the observed products.

TABLE 1.8

Observed Product Ratios for Reactions of Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12) with Pyridine in 0.1 M Potassium Chloride at 25.0°C

Ethenesulfonyl Chloride (8)

initial sulfonyl chloride concentration: 1.6×10^{-2} M

pH	[pyridine](a) (M)	X(b)	% betaine(c)
3.0	1.0×10^{-3}	22	80
3.0	5.3×10^{-3}	110	77
4.0	1.0×10^{-2}	220	80
4.0	1.0×10^{-2}	220	83(d,e)
5.0	5.0×10^{-2}	1000	85(f)

trans-1-Propene-1-sulfonyl Chloride (12)

initial sulfonyl chloride concentration: 9×10^{-3} M

pH	[pyridine] M	X	% betaine
4.0	1.6×10^{-2}	20	56

a) concentration of free pyridine initially present ($pK_a = 5.35$).

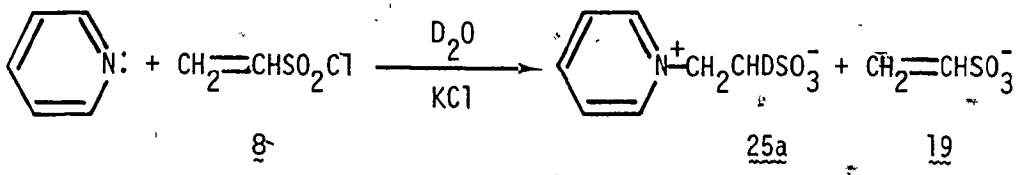
b) $X = k_B$ pyridine $/k_1$, where for 8 $k_B = 28\ M^{-1}s^{-1}$, $k_1 = 1.32 \times 10^{-3}\ s^{-1}$
12 $k_B = 1.5\ M^{-1}s^{-1}$, $k_1 = 1.22 \times 10^{-3}\ s^{-1}$

c) % betaine = 100 (amount of betaine/amount of betaine + amount of alkenesulfonate anion) where amount of betaine is estimated by ^1H n.m.r. integration.

d) isolated yield using Rexyn 300 deionizing resin.

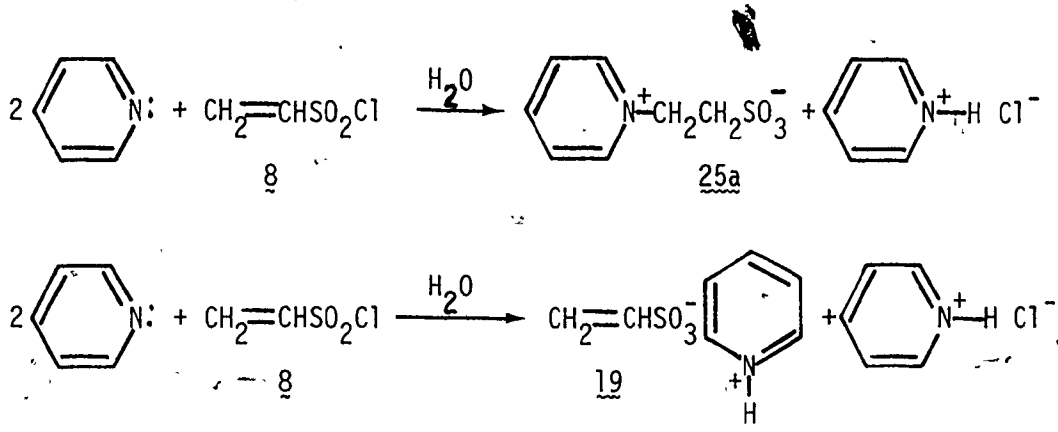
e) sulfonyl chloride concentration: 1.0×10^{-2} M

f) sulfonyl chloride concentration: 3.2×10^{-3} M



This experiment allowed the determination of the isotope effect for the trapping of a common intermediate by H_2O versus D_2O in the reaction of ethenesulfonyl chloride (8) with pyridine at 25.0° (k_H/k_D ∿1.9).*

The formation of the observed products in the reactions of the sulfonyl chlorides with pyridine in water allows the following stoichiometric equations to be generated (shown below for the reaction of 8 with pyridine).



From these equations it is evident that formation of 25a results in the formation of 1 equivalent of acid while formation of 19 liberates 2 equivalents.

The rates of the reactions of 8 and 12 with pyridine were studied using the pH-stat technique. Observed pseudo first order rate constants (k_ψ) were obtained for various initial concentrations of pyridine at

*See Appendix 4.

25.0°C. These plots were observed to be linear to ≥90% reaction, indicating that the reactions were first order in the sulfonyl chloride. The rate constants and the end point titres for the kinetic runs are given in Table 1.9. The end point titres were found to generally agree with the product ratio expected from the relative concentration of the reagents in the kinetic run (within experimental error of the initial substrate concentration).

Although in principle the product ratios for the reactions of 8 and 12 with pyridine could be determined from the end point titres from each kinetic run, the errors associated with the preparation of the stock solutions of the sulfonyl chlorides (taken with the unavoidable preliminary hydrolysis of the sulfonyl chloride in the stock solution) made this method inaccurate for this purpose. Therefore product ratios were determined by analysis (using ^{1}H n.m.r. spectroscopy) of the crude reaction mixtures obtained in larger scale reactions. Several ratios of observed end point titres to theoretical end point titres are given (as F values) in Table 1.9.

From these data (along with the value of k_1 previously determined for each sulfonyl chloride), second order plots of k_ψ versus pyridine concentration were constructed for the reactions of pyridine with 8 and 12. These plots were also observed to be linear, with the plot of 8 shown in Figure 1.5. The linearity of these plots indicated a first order dependence of the reaction rate on

the concentration of free pyridine.

The observed kinetic behavior of the sulfonyl chlorides (8) and (12) in aqueous pyridine solution resulted in the following rate law for their reactions in water:

$$\frac{-d[S]}{T} = k_1[S] + k_{OH^-}[S][OH^-] + k_B[S][B]$$

where $[S]$ = sulfonyl chloride concentration

$[OH^-]$ = hydroxide ion concentration

$[B]$ = free pyridine concentration

Since the term $k_{OH^-}[OH^-]$ was insignificant in the pH range of these experiments, this rate law simplifies to:

$$\frac{-d[S]}{dt} = k_1[S] + k_B[S][B]$$

and

$$k_\psi = k_1 + k_B[B]$$

for these reactions.

TABLE 1.9

Observed Pseudo First Order Rate Constants for the Reactions of Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12) with Pyridine in Water at 25.0° C

Ethenesulfonyl Chloride (8)

pH	$10^4 \cdot$[pyridine] (M)[a]	$10^2 \cdot k_\psi (s^{-1})$	$k_B (M^{-1}s^{-1})$[b]	F[c]
2.7	1.11	0.384	23	0.90
2.7	1.66	0.548[d]	23	0.75
3.0	1.11	0.455	29	0.95
3.5	3.46	1.04	26	0.95
3.5	4.50	1.44	29	0.75
3.5	5.54	1.68	28	0.80

mean $k_B = 26 \pm 3$[e] $M^{-1}\ s^{-1}$

trans-1-Propene-1-sulfonyl Chloride (12)

pH	$10^3 \cdot$[pyridine] (M)	$10^3 \cdot k_\psi (s^{-1})$	$k_B (M^{-1}s^{-1})$	F
4.0	1.06	3.24	1.9	0.95
4.5	2.30	4.74	1.5	0.90
4.5	3.07	5.92	1.5	0.90

mean $k_B = 1.6 \pm 0.2$[e] $M^{-1}\ s^{-1}$

a) concentration of free pyridine.

b) calculated from $k_\psi = k_1 + k_B B$.

c) F = observed end point titre (mL)/titre (mL) calculated for 100% uncatalysed hydrolysis of the sulfonyl chloride.

d) straight to >80% reaction.

e) standard deviation.

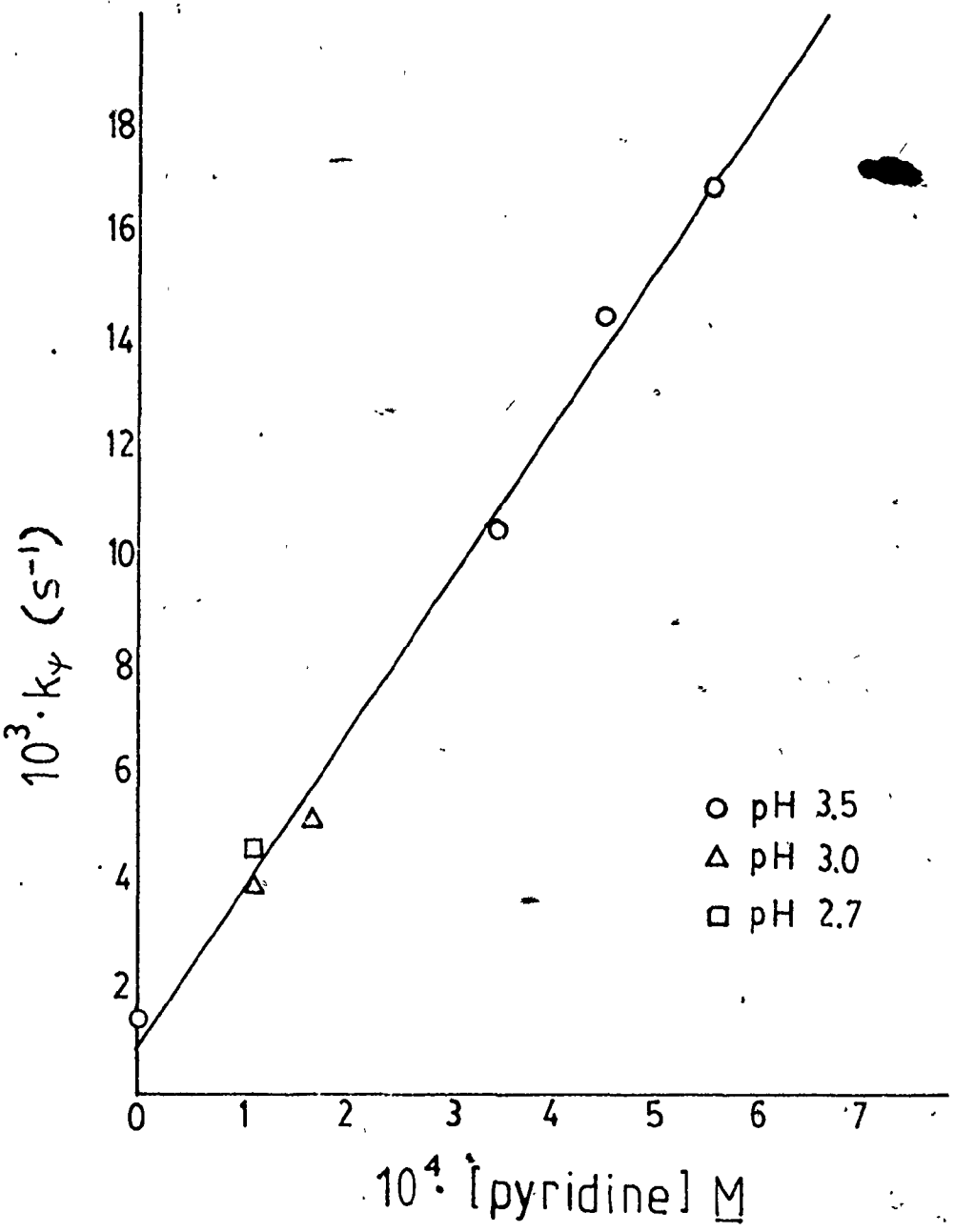


FIGURE 1.5 Second Order Plot for Reaction of Ethenesulfonyl Chloride (8) with Pyridine in Water at 25.0°C

The observed order for the reaction of 8 or 12 with pyridine is consistent with the mechanism for betaine (25) formation proposed by Le Berre et al (39) for reaction of 8 with pyridines in acetic acid (see Scheme 1.7). In the present work, water would replace acetic acid as the solvent. The rate determining S_N2' reaction of pyridine upon the sulfonyl chloride (8) generates an intermediate pyridiniosulfene (X = H, 16a) which is subsequently trapped by the solvent to eventually generate the betaine (25a). Le Berre et al did not report the formation of any ethenesulfonate anion (19) in their reactions, whereas the present results showed up to 35% of the total products was the alkenesulfonate anion. Similar results were observed by King and Loosmore (40) in the pyridine catalysed alcoholysis reactions of 8 and 12.

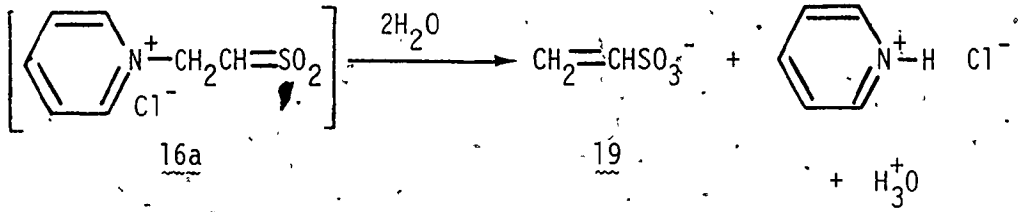
Several possibilities exist for the mechanism of formation of the alkenesulfonate anion products in these experiments. The three mechanisms which are considered to be the most likely means of generating the alkenesulfonates are: a) from the pyridiniosulfene (16) intermediate (formally described as the vinylogous nucleophilic catalysis mechanism); b) general base catalysed hydrolysis of the sulfonyl chloride; and c) direct (S_N2) nucleophilic catalysed hydrolysis at sulfonyl sulfur, proceeding through an intermediate sulfonylpyridinium ion. These mechanisms are illustrated in Scheme 1.13 for clarity and for further discussion.

Mechanism (a) in this scheme will be referred to as the "common mechanism", where 16 generates both the betaine (25) and ethenesulfonate anion (19) products. The other mechanisms ((b) and (c)) assume that the betaine (25) is generated from the pyridiniosulfene (16) intermediate

SCHEME 1.13

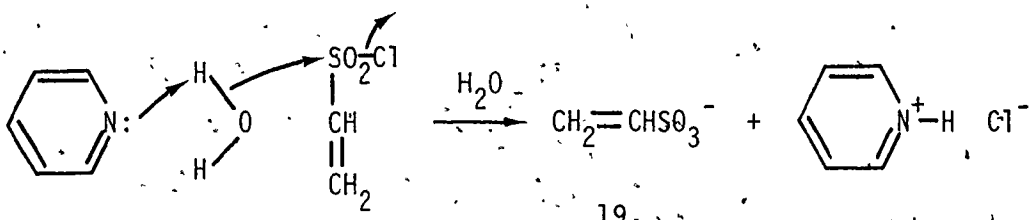
Possible Mechanisms of Reaction of Pyridine with Ethenesulfonyl Chloride (8) in Water

a) Vinylogous Nucleophilic Catalysis



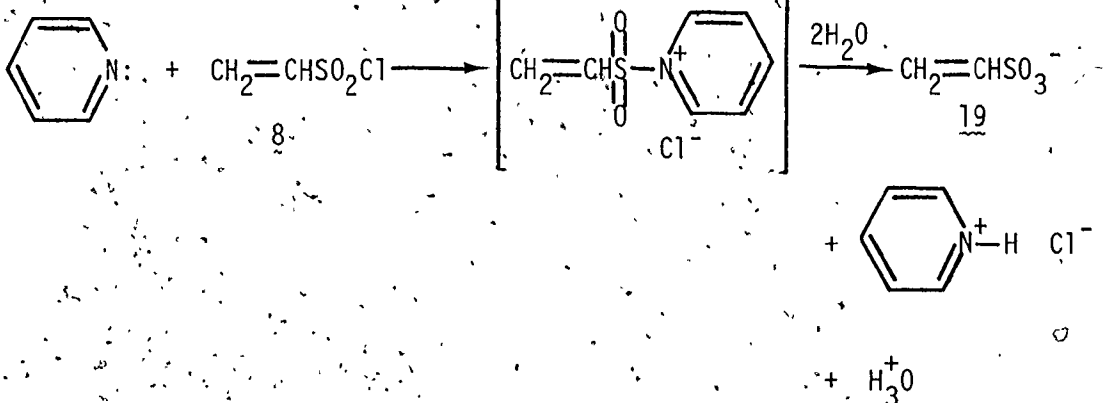
16a 19

b) General Base Catalysis



8 19

c) "Direct" Nucleophilic Catalysis

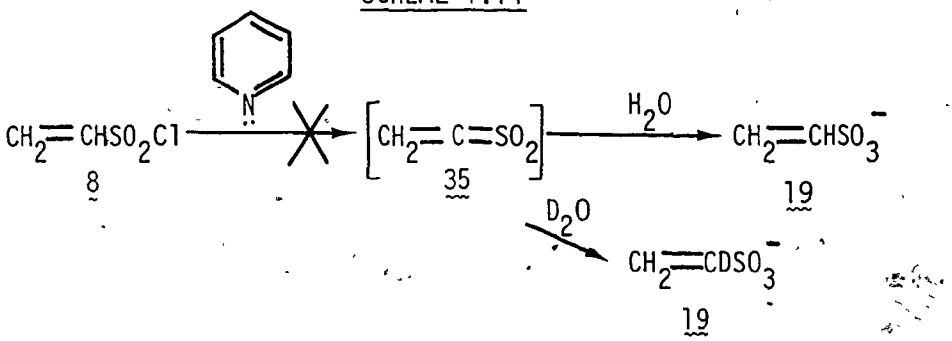


8 19

(but the alkenesulfonate anion is not). Therefore these mechanisms will be referred to as "separate mechanisms" in the discussion which follows.

A mechanism whereby the alkenesulfonate anion is generated from a cumulated sulfene (35) intermediate may be discarded from the results of the reaction of 8 with pyridine in D_2O. Only undeuterated ethenesulfonate anion (19) was isolated, a result contrary to that expected (5) if 35 were generated in a deuterated medium, as shown in Scheme 1.14.

SCHEME 1.14



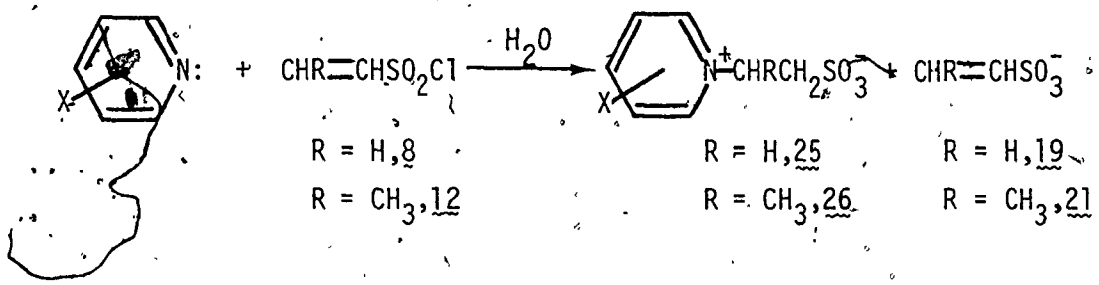
Distinguishing which of the mechanisms presented in Scheme 1.13 is responsible for the formation of the alkenesulfonate anion product will be the focus of the next section.

(e) Reactions of Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12) with Substituted Pyridines in Water Containing 0.1 M Potassium Chloride at 25.0°C

The rates of the reactions of ethenesulfonyl chloride (8) and trans-1-propene-1-sulfonyl chloride (12) with a series of 15 substituted pyridine bases (including 5 pyridines having ortho substituents) were investigated by the method already described. The observed pseudo first order rate constants (k_ψ) as a function of the concentration of the

various free pyridine bases are given in Tables 1.10 and 1.11. From these data, "second order plots" of k_ψ versus concentration of free base were constructed for each reaction of a base with 8 and 12. These plots were observed to be linear in all cases, so that the rate law presented earlier evidently applies to the reactions with the substituted pyridines as well. The second order rate constants (k_B's) for these reactions are given in Tables 1.12 and 1.13.

The reaction products were determined from preparative scale reactions of the substituted pyridines with 8 and 12 under the conditions described in the Experimental section. ^{1}H n.m.r. analysis of the crude reaction mixture indicated the presence of the appropriate pyridine betaine along with the alkenesulfonate anion in all reactions. The substituted pyridine betaines were all identified by comparison with the ^{1}H n.m.r. spectra of samples of authentic betaines (prepared by the method of Le Berre (39)).



Again there were no signals observed in the ^{1}H n.m.r. spectrum of the product mixtures which corresponded to either isethionate anion (20) or 2-hydroxypropane-1-sulfonate anion (22). The product ratios obtained in these experiments are represented by parameter q (q = %betaine/%betaine + %alkenesulfonate anion)). This parameter was corrected for any alkenesulfonate generated from the uncatalysed

TABLE 1.10

Observed Pseudo First Order Rate Constants for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in Water Containing 0.1 M Potassium Chloride at 25.0°C

Pyridine	pK_a [a]	$10^4 \cdot$[Pyridine] [b] (M)	pH	$10^2 \cdot k_\psi$ (s^{-1})
3,4-$(CH_3)_2$	6.68	0.372	4.0	0.532
		0.743	4.0	0.837
4-CH_3	6.17	0.960	4.0	0.585
		1.38	4.0	0.903
		2.76	4.0	1.71
3,5-$(CH_3)_2$	6.13	1.30	4.0	0.903
		2.58	4.0	1.71
		3.00	4.5	1.98
3-CH_3	5.68	4.23	4.0	1.73
		8.46	4.0	3.31
4-CH_2CH_3	6.15	1.24	4.0	0.767
		2.49	4.0	1.46
3-$CONH_2$	3.47	3.92	2.0	0.390
		6.45	2.0	0.555
		47.2	2.75	3.05
3-CN	1.45	101	3.0	2.11
		137	3.0	2.67
		238	3.0	4.67
3-$NHCOCH_3$	4.50	3.38	3.0	0.964
		4.45	3.0	1.20
		6.99	3.0	1.70
4-CO_2CH_3	3.30	20.0	2.5	1.81
		35.1	2.8	2.84
		48.7	3.0	3.60
2,6-$(CH_3)_2$	6.87	61.3	6.0	0.169
		494	7.0	0.351
		800	8.0	0.536

TABLE 1.10 (CONTINUED)

Pyridine	pK_a [a]	$10^4 \cdot [Pyridine]$ [b] (M)	pH	$10^2 \cdot k_\psi$ (s^{-1})
2-CH_3	6.15	8.09	5.0	0.617
		13.5	5.0	0.988
		27.0	5.0	1.98
2-CH_2CH_3	6.00	11.9	5.0	0.367
		19.9	5.0	0.510
		31.8	5.0	0.883
2,4,6-$(CH_3)_3$	7.40	121	8.0	0.245 [c]
		212	8.0	0.370 [c]
		302	8.0	0.463 [c]
Benzo[b]- [d]	4.80	6.95	4.0	0.270
		13.9	4.0	0.407

a) determined from the titration curve of each pyridine base in 0.1 M KCl by the half neutralization technique, except for 3-cyanopyridine.

b) free pyridine base concentration.

c) reaction followed to ~85% reaction.

d) i.e. quinoline.

TABLE 1.11

Observed Pseudo First Order Rate Constants for the Reactions of trans-1-Propene-1-sulfonyl Chloride (12) with Substituted Pyridines in Water Containing 0.1 M Potassium Chloride at 25.0°C

Pyridine	pK_a[a]	$10^3 \cdot$[Pyridine] (M)[b]	pH	$10^3 \cdot k_\psi$ (s^{-1})
3,4-$(CH_3)_2$	6.68	0.272	5.0	2.94
		0.830	5.5	6.02
		1.10	5.5	7.30
4-CH_3	6.17	0.976	5.0	4.35
		1.30	5.0	5.13
		1.63	5.0	5.93
3,5-$(CH_3)_2$	6.13	0.904	5.0	4.92
		1.20	5.0	5.86
		1.51	5.0	6.85
3-CH_3	5.68	0.960	4.5	3.47
		1.28	4.5	4.09
		2.68	5.0	6.57
3-$NHCOCH_3$	4.50	3.14	4.0	5.80
		4.84	4.0	7.68
		7.60	4.0	10.7
4-CO_2CH_3	3.30	4.88	3.0	4.12[c]
		17.9	3.5	9.25
3-CN	1.45	24.4	4.0	4.20
		46.0	4.0	7.01
		74.2	4.0	9.90
2-CH_3	6.15	13.4	7.0	3.30
		17.9	7.0	4.73
		31.3	7.0	6.23
3-$CONH_2$	3.47	7.22	4.0	5.47
		15.4	4.0	1.06

TABLE 1.11 (CONTINUED)

Pyridine	pK_a	$10^3 \cdot$[Pyridine](M)[b]	pH	$10^3 \cdot k_\psi$ (s^{-1})
2-CH_2CH_3	6.00	15.9	7.0	3.32[c]
		31.8	7.0	4.61
2,6-$(CH_3)_2$	6.87	48.0	8.0	0.97
Benzo[b]-[d]	4.80	11.2	6.0	2.24
		19.1	6.0	2.64
		31.9	6.0	3.62

a) as determined from titration curve.

b) free pyridine concentration.

c) reaction followed to ≥80% reaction.

d) i.e. quinoline.

TABLE 1.12

Second Order Rate Constants for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 0.1 M Potassium Chloride at 25.0° C

Pyridine	pK_a	$k_B(M^{-1}s^{-1})$(a)	r(b)	log k_B
3,4-$(CH_3)_2$	6.68	95	0.997	1.98
3,5-$(CH_3)_2$	6.13	62	0.999	1.79
4-CH_3	6.17	58	0.997	1.76
4-CH_2CH_3	6.15	53	0.990	1.72
3-CH_3	5.68	38	0.997	1.58
H	5.35	28	0.998	1.44
3-$NHCOCH_3$	4.50	22	0.998	1.35
3-$CONH_2$	3.47	6.2	0.999	0.79
4-CO_2CH_3	3.30	7.2	0.996	0.86
3-CN	1.45	1.9	0.999	0.28
2-CH_3	6.15	6.9	0.999	0.84
2,6-$(CH_3)_2$	6.87	0.05	0.997	-1.31
2,4,6-$(CH_3)_3$	7.40	0.11	0.997	-0.96
Benzo[b]-	4.80	2.0	0.999	0.30
2-CH_3CH_2	6.00	2.3	0.990	0.36

a) determined by least squares analysis of the data in Table 1.10 taken with the mean value of k_1 ($1.32 \times 10^{-3}s^{-1}$) as the y-intercept.

b) correlation coefficient.

TABLE 1.13

Second Order Rate Constants for the Reactions of trans-1-Propene-1-sulfonyl Chloride (12) with Substituted Pyridines in 0.1 M Potassium Chloride at 25.0°C

Pyridine	pK_a	$k_B(M^{-1}s^{-1})$(a)	r(b)	log k_B
3,4-$(CH_3)_2$	6.68	5.5	0.999	0.74
3,5-$(CH_3)_2$	6.13	3.8	0.998	0.58
4-CH_3	6.17	2.9	0.997	0.46
3-CH_3	5.68	2.0	0.996	0.30
H	5.35	1.5	0.995	0.18
3-$NHCOCH_3$	4.50	1.2	0.996	0.08
3-$CONH_2$	3.47	0.57	0.999	-0.24
4-CO_2CH_3	3.30	0.44	0.994	-0.36
3-CN	1.45	0.12	0.999	-0.92
2-CH_3	6.15	0.16	0.988	-0.80
2-CH_2CH_3	6.00	0.10	0.990	-0.96
Benzo[b]-	4.80	0.074	0.996	-1.13

a) determined by least squares analysis of the data in Table 1.11 taken with the mean value of k_1 ($1.22 \times 10^{-3}s^{-1}$) as the y-intercept.

b) correlation coefficient.

hydrolysis reaction of the sulfonyl chloride, and these values are given in Tables 1.14 and 1.15. Often the corrected value of q did not differ from the experimentally observed product ratios by more than 1 or 2%.

Brönsted plots of log k_B versus pK_a were constructed for each of the sulfonyl chlorides, and are illustrated in Figures 1.6, 1.7. In both plots, linear relationships were observed for the reactions performed with the unhindered pyridine bases.

The equation of the line for the reactions with ethenesulfonyl chloride (8) was determined by least squares analysis to be log k_B = 0.32 (pK_a) - 0.22 with r = 0.993. For trans-1-propene-1-sulfonyl chloride the equation was determined to be log k_B = 0.30 (pK_a) - 1.34 with r = 0.991. The hindered pyridines were observed to fall considerably below these lines. The magnitudes of their deviations from these lines were calculated, and are presented in Table 1.16 along with the ratios of the k_B's for the hindered pyridines relative to pyridine itself.

It is evident from the equations of the lines for 8 and 12 that the Brönsted β coefficients are identical within experimental error. However, the line established for the reactions of the unhindered pyridines with 8 is displaced upwards from the line established for 12. The differences in the k_B values for reactions with 8 and 12 with a given pyridine base range from a factor of 11 (for nicotinamide) to a factor of 20 (for 4-picoline) for the unhindered bases. The hindered pyridine bases also reacted significantly faster with ethenesulfonyl chloride (8) than with 1-propene-1-sulfonyl chloride (12).

TABLE 1.14

Product Ratios for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 0.1 M Potassium Chloride at 25.0°C

Pyridine	pK_a	corrected q[(a)]
3,4-$(CH_3)_2$	6.68	0.90
3,5-$(CH_3)_2$	6.13	0.84
4-CH_3	6.17	0.88
4-CH_2CH_3	6.15	0.84
3-CH_3	5.68	0.87
H	5.35	0.81
3-$NHCOCH_3$	4.50	0.67
3-$CONH_2$	3.47	~0.5
4-CO_2CH_3	3.30	0.52
3-CN	1.45	0.17
2-CH_3	6.15	0.57
2-CH_2CH_3	6.00	0.90
2,6-$(CH_3)_2$	6.87	0.70
2,4,6-$(CH_3)_3$	7.40	0.67
Benzo [b]-	4.80	0.52

a) $$\text{corrected q} = \frac{\%\ \text{betaine}}{100\left(1 - \frac{k_1}{k_B[\text{pyridine}]}\right)}$$

where $$\%\ \text{betaine} = 100 \cdot \left(\frac{\text{amount of betaine}}{\text{amount of betaine} + \text{amount of alkenesulfonate}}\right)$$

as determined by ^1H n.m.r. integration.

TABLE I.15

Product Ratios for the Reactions of trans-1-Propene-1-sulfonyl Chloride (12) with Substituted Pyridines in 0.1 M Potassium Chloride at 25.0°C

Pyridine	pK_a	corrected q
3,4-$(CH_3)_2$	6.68	0.75
3,5-$(CH_3)_2$	6.13	0.70
4-CH_3	6.17	0.74
3-CH_3	5.68	0.69
H	5.35	0.58
3-$NHCOCH_3$	4.50	0.45
3-$CONH_2$	3.47	(a)
4-CO_2CH_3	3.40	0.27
3-CN	1.45	0.09
2-CH_3	6.15	0.40
2-CH_2CH_3	6.00	0.75
Benzo [b]-	4.80	0.50

(a) unavailable due to difficulties in extracting nicotinamide from the reaction mixture.

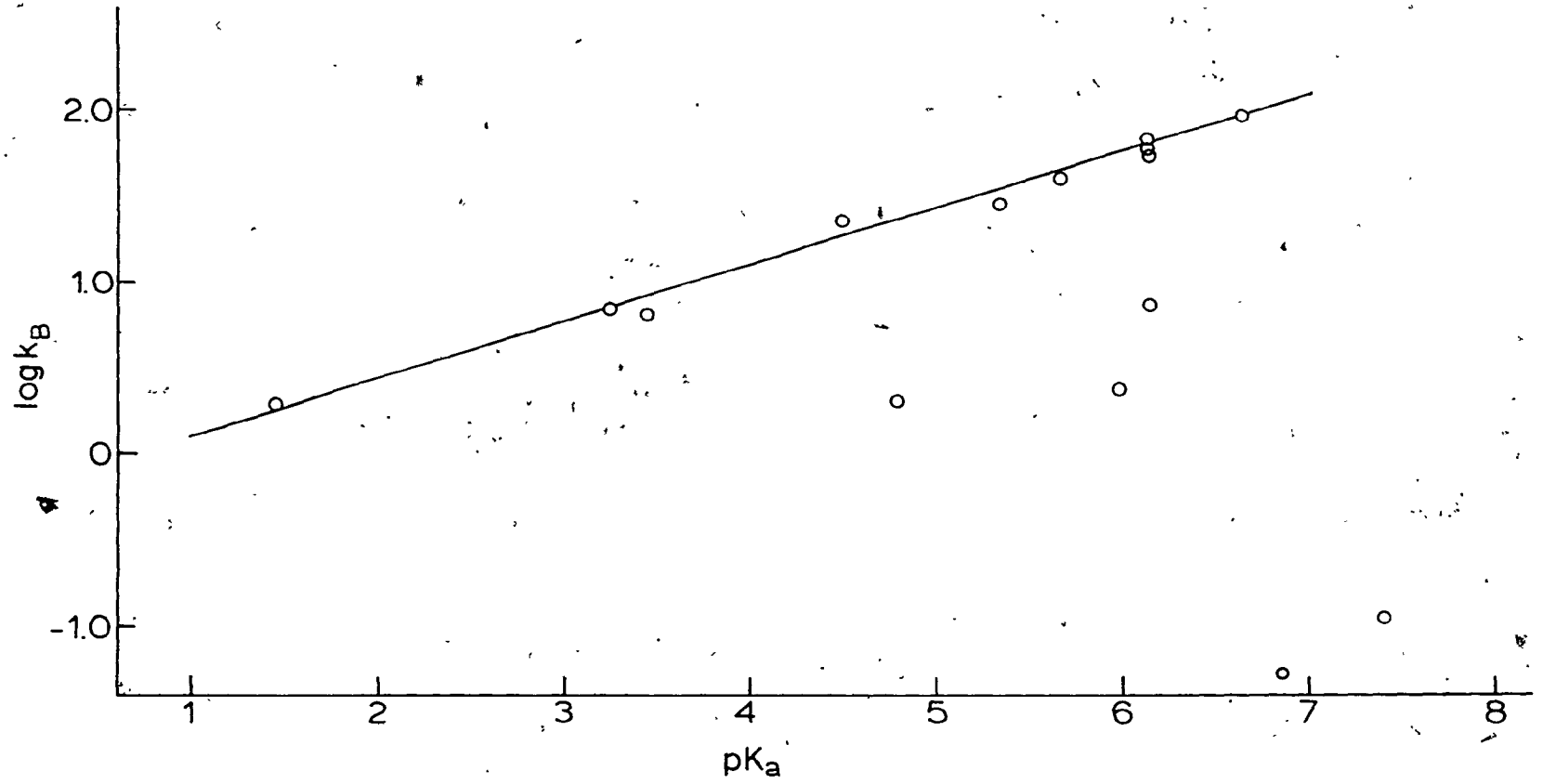


FIGURE 1.6 Brönsted Plot for Reaction of Ethenesulfonyl Chloride (8) with Substituted Pyridines in Water at 25.0°C

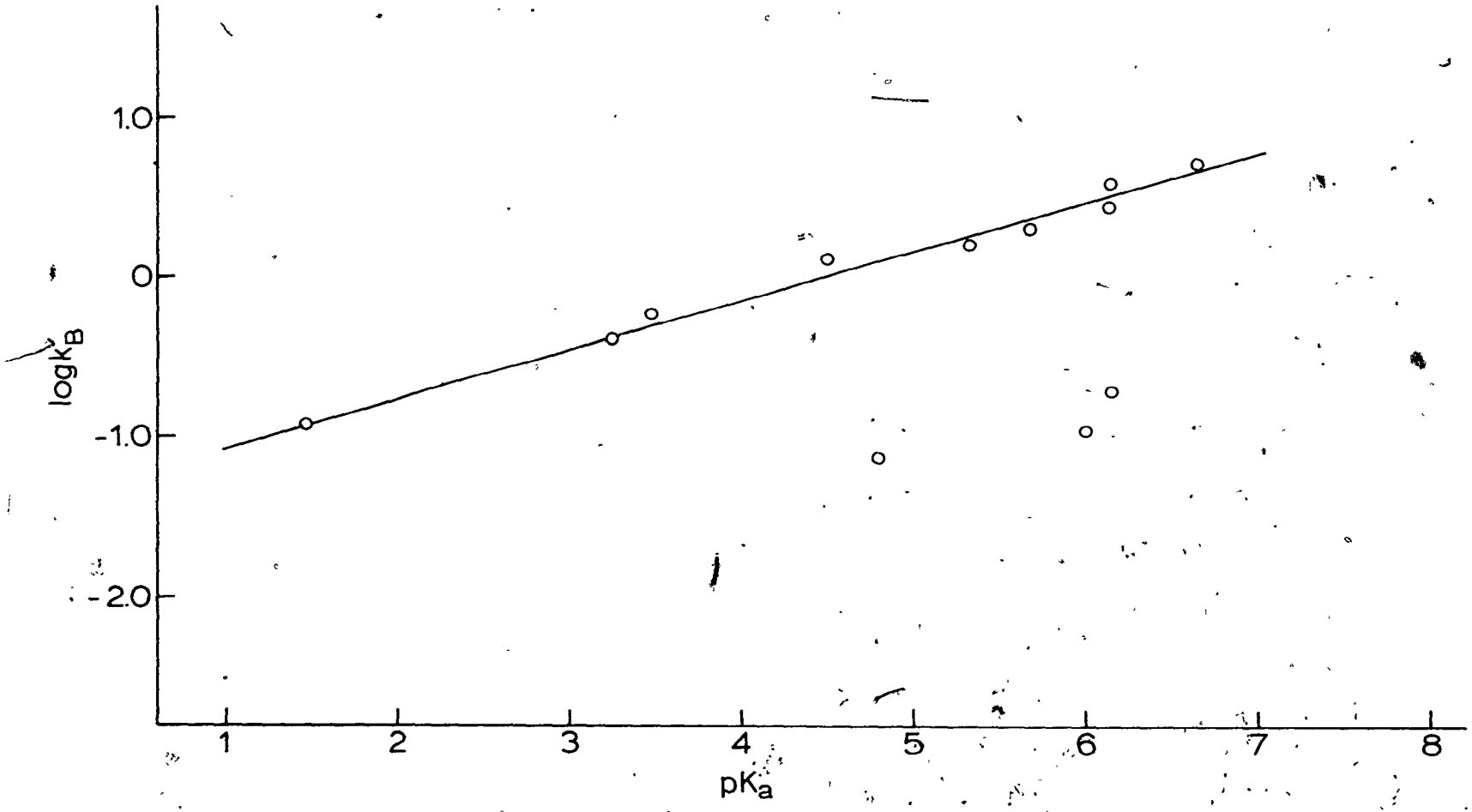


FIGURE 1.7 Brönsted Plot for Reaction of trans-1-Propene-1-sulfonyl Chloride (12) with Substituted Pyridines in Water at 25.0°C

TABLE 1.16

Deviations from the Brönsted Equation for Reactions of Substituted Pyridines with Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12) in 0.1 M Potassium Chloride at 25.0°C

Ethenesulfonyl Chloride (8)[a]

Pyridine	pK_a	log k_B	Δ ($M^{-1}s^{-1}$)[b]	$\frac{k_B(\text{pyridine})}{k_B(\text{subst. pyridine})}$
2-CH_3	6.15	+0.84	8.1	4.1
2-CH_2CH_3	6.00	+0.36	23	12
2,6-$(CH_3)_2$	6.87	-1.31	2.1×10^3	5.6×10^2
2,4,6-$(CH_3)_3$	7.40	-0.96	1.4×10^3	2.5×10^2
Benzo [b]-	4.80	+0.41	8.4	14

trans-1-Propene-1-sulfonyl Chloride (12)[c]

Pyridine	pK_a	log k_B	Δ ($M^{-1}s^{-1}$)	$\frac{k_B(\text{pyridine})}{k_B(\text{subst. pyridine})}$
2-CH_3	6.15	-0.80	20	9.4
2-CH_2CH_3	6.00	-0.96	26	15
Benzo [b]-	4.80	-1.13	17	20

a) Brönsted equation: $\log k_B = 0.32\ (pK_a) - 0.22$.

b) Δ refers to the difference between the observed k_B and a calculated k_B for an unhindered pyridine of identical pK_a.

c) Brönsted equation: $\log k_B = 0.30\ (pK_a) - 1.34$.

(f) Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in Water Containing 0.1 M Potassium Chloride at 45.0° C

The relative rates of the reactions of ethenesulfonyl chloride (8) with several substituted pyridines at 45.0° were also determined in the manner previously described. These results are given in Table 1.17, and the second order rate constants (k_B's) are given in Table 1.18. The Brönsted plot of log k_B versus pK_a (shown in Figure 1.8) gave the equation of the line described by the unhindered bases as log k_B = 0.32 (pK_a) + 0.32, with r = 0.988. The deviations of the two hindered pyridines are given in Table 1.19. The values of the Brönsted β coefficients, as well as the magnitudes of the deviations from the line exhibited by 2-picoline and 2,6-lutidine, are identical (within experimental error) to those values obtained for the reactions of 8 at 25.0°.

The activation parameters for the reactions of ethenesulfonyl chloride (8) with several substituted pyridines in water were estimated from the data obtained at 25.0° and 45.0°. Eyring plots of $\ln(k_B/T)$ versus (1/T) were constructed for each base, and the results of these plots are given in Table 1.20. The activation enthalpies ($\Delta H^{\ddagger}$) and entropies ($\Delta S^{\ddagger}$) reported here must be employed with due caution since they were derived from only 2 point plots. The errors associated with these parameters are the maximum errors as calculated by the method of Wiberg (53).

General Discussion of Reaction Mechanism

In the study of the hydrolysis reactions of 8 and 12 in the absence of pyridine bases, it was established that the rates of the direct attack of water on the sulfonyl group of 8 and 12 were identical.

TABLE 1.17

Observed Pseudo First Order Rate Constants for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 0.1 M Potassium Chloride at 45.0°C

Pyridine	pK_a	$10^4 \cdot [Pyridine]$ (M)[a]	pH	$10^2 \cdot k_\psi$ (s^{-1})
3,4-$(CH_3)_2$	6.43	0.0525	3.2[b]	0.866
		0.105	3.2	1.02
		0.132	3.0	1.08
4-CH_3	6.03	0.295	3.2	1.38
		0.608	3.2	1.92
3-CH_3	5.68	0.431	3.0	1.34
		0.862	3.2	2.09
		1.02	3.2	2.21
H	5.28	0.649	3.0	1.28
		2.05	3.2	2.38
3-$NHCOCH_3$	4.55	2.06	3.0	2.48
		3.14	3.2	3.84
		4.65	3.2	4.60
3-$CONH_2$	3.55	10.1	3.2	3.17
		15.2	3.2	4.39
3-CN	1.45	49.1	3.2	3.26
		85.0	3.2	6.25
2-CH_3	6.00	1.21	4.0	1.21
		2.02	4.0	1.42
		3.03	4.0	1.65
2,6-$(CH_3)_2$	6.67	4.93	8.0[c]	1.91
		8.29	8.0	2.26

a) free pyridine base conc.
b) $k_1 = 7.2 \times 10^{-3} s^{-1}$ at pH 3.0.
c) $k_1 = 1.08 \times 10^{-2} s^{-1}$ at pH 8.0.

TABLE 1.18

Second Order Rate Constants for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 0.1 M Potassium Chloride at 45.0°C

Pyridine	pK_a	$k_B(M^{-1}s^{-1})$(a)	r	log k_B
3,4-$(CH_3)_2$	6.43	277	0.994	2.44
4-CH_3	6.03	197	0.997	2.29
3-CH_3	5.68	151	0.997	2.18
H	5.28	81	0.999	1.91
3-$NHCOCH_3$	4.55	86	0.990	1.93
3-$CONH_2$	3.55	24	0.999	1.38
3-CN	1.45	6.4	0.991	0.81
2-CH_3	6.00	31	0.990	1.49
2,6-$(CH_3)_2$	6.67	0.15	0.993	-0.82

a) determined by least squares analysis of plots of k_ψ versus free pyridine concentration (data given in Table 1.17).

TABLE 1.19

Deviations of Hindered Pyridines from the Brönsted Equation for Reactions of Substituted Pyridines with Ethenesulfonyl Chloride (8) in 0.1 M Potassium Chloride at 45.0°C

Pyridine	pK_a	log k_B	Δ $(M^{-1}s^{-1})$	$\frac{k_B(\text{pyridine})}{k_B(\text{subst. pyridine})}$
2-CH_3	6.00	+1.49	5.6	2.6
2,6-$(CH_3)_2$	6.67	-0.82	$1.88 \times 10^{+3}$	5.4×10^{2}

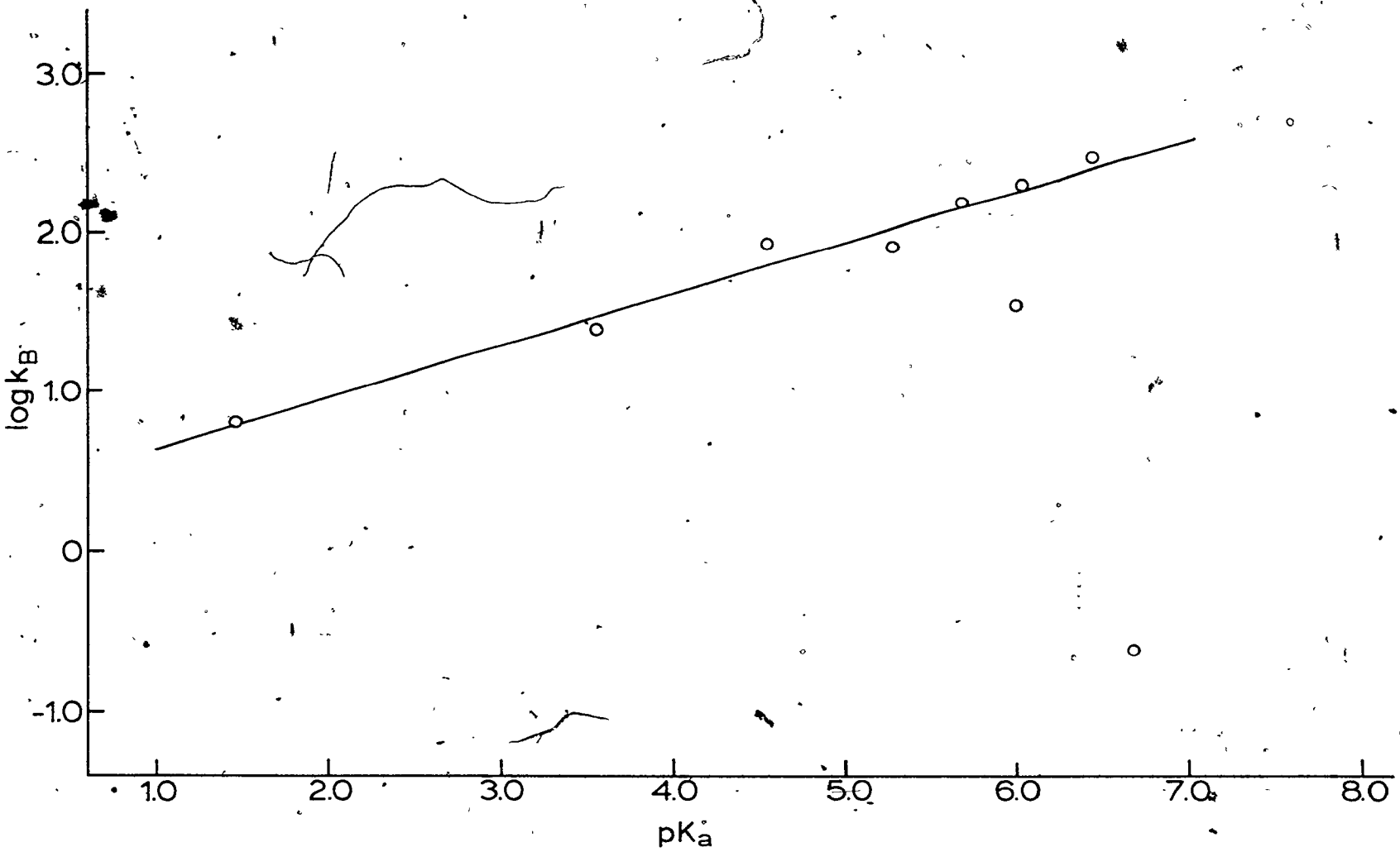


FIGURE 1.8 Brönsted Plot for Reaction of Ethenesulfonyl Chloride (8) with Substituted Pyridines in Water at 45.0°C

TABLE 1.20

Eyring Plots and Activation Parameters for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 0.1 M Potassium Chloride

Pyridine	$\ln(k_B/298)$	$\ln(k_B/318)$	$\Delta H^{\ddagger}$(kcal mol^{-1})	$-\Delta S^{\ddagger}$(cal deg^{-1} mol^{-1})
3,4-$(CH_3)_2$	1.14	0.12	9.5 ± 1.1	17.7 ± 3.8
4-CH_3	1.63	0.48	10.9	14.0
3-CH_3	2.06	0.74	12.4	10.0
H	2.36	1.37	9.4	20.4
3-CN	5.06	3.91	10.8	21.0
3-$CONH_2$	3.87	2.58	12.1	14.0
3-$NHCOCH_3$	2.61	1.31	12.2	11.3
2-CH_3	3.77	2.33	13.5	9.2
2,6-$(CH_3)_2$	8.70	7.66	9.7	31.8

within experimental error. For the reactions of the sulfonyl chlorides with hydroxide ion (as represented by their k_{OH^-} values) which were also concluded to proceed by direct nucleophilic attack at sulfur, only a small difference in k_{OH^-} values was observed. In this context, if the reactions of 8 and 12 with the substituted pyridines to produce the alkenesulfonate anions were proceeding by direct nucleophilic attack at sulfur (path C, Scheme 1.13), then little or no difference in k_B values between 8 and 12 for a given base would have been anticipated. This was clearly not the observed result.

To further test the suitability of mechanism (C) to describe the generation of the alkenesulfonate products, the corrected q values may be employed to estimate the relative second order rate constants for these reactions with each pyridine base. Scheme 1.15 illustrates the "separate mechanism" (corresponding to mechanism (C)) for the formation of the observed reaction products with 8. In this scheme k_N is the second order rate constant for S_N2' attack on carbon, while k_S is the rate constant for direct attack at sulfonyl sulfur.

The partitioned rate constants were calculated from the observed value of k_B and the corrected value of q for the reaction of 8 with each base, and are given in Table 1.21. Brönsted plots of log k_N versus pK_a and log k_S versus pK_a were constructed, and the equations of the lines were determined (by least squares analysis in the usual manner) to be log k_N = 0.45 (pK_a) - 1.05 with r = 0.993 and log k_S = 0.14 (pK_a) + 0.27 with r = 0.938, respectively. The β value of 0.14 for the generation of the alkenesulfonate product by direct nucleophilic attack at sulfur does not compare favorably with that of 0.45 obtained for the pyridine catalysed hydrolysis of benzenesulfonyl chloride, a process

SCHEME 1.15

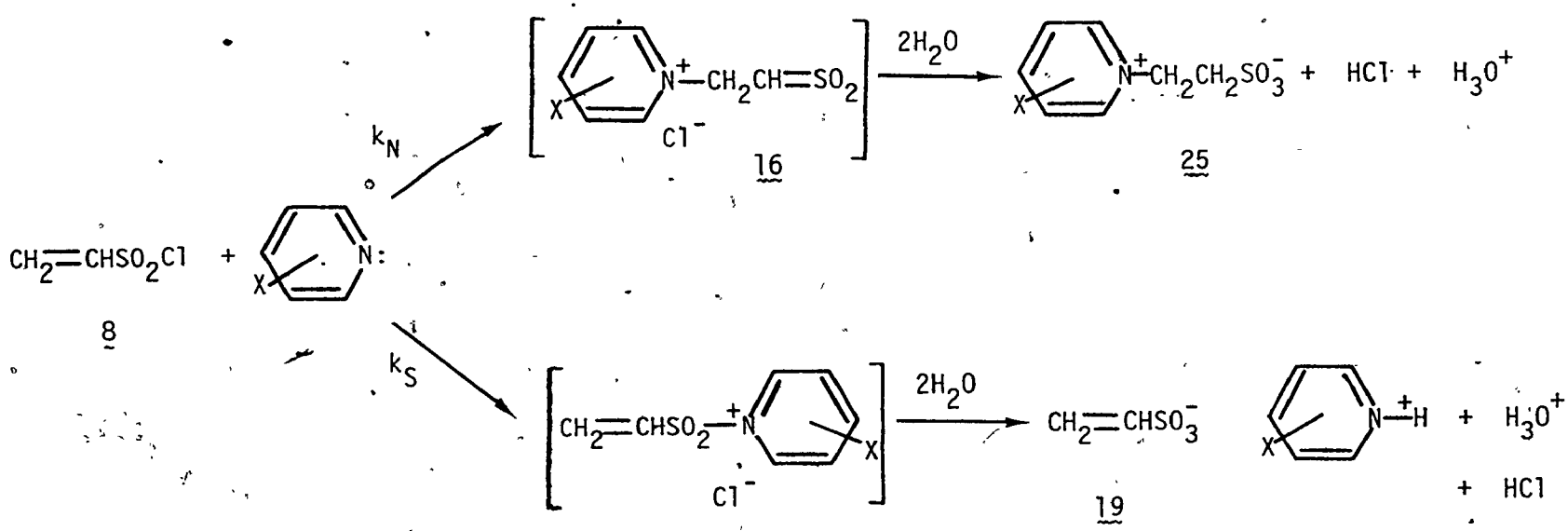


TABLE 1.21

Partitioned Second Order Rate Constants for the Reaction of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 0.1 M Potassium Chloride at 25.0°C

Pyridine	$k_B(M^{-1}s^{-1})$	corrected q[a]	$k_S(M^{-1}s^{-1})$[c]	$k_N(M^{-1}s^{-1})$[b]
3,4-$(CH_3)_2$	95 ± 5%	0.90	9	86
3,5-$(CH_3)_2$	62	0.85	9	53
4-CH_3	58	0.88	7	51
4-CH_2CH_3	53	0.87	7	46
3-CH_3	38	0.84	6	32
H	28	0.81	5	23
3-$NHCOCH_3$	22	0.67	7	15
3-$CONH_2$	6.2	0.5	3.1	3.1
3-CO_2CH_3	7.2	0.52	3.5	3.7
3-CN	1.9	0.17	1.6	0.3

a) from Table 1.14.

b) k_N = corrected q·k_B

c) k_S = (1 - corr. q)·k_B

concluded to be proceeding by nucleophilic catalysis at sulfonyl sulfur (24). The correlation coefficient (r) for this plot is also not a very satisfying value for a correlation of this type. These observations, when taken with the 20 fold rate difference between k_B's for 8 and 12 argue strongly against the "direct" S_N2 mechanism (path (c)) for the generation of the alkenesulfonate products in these reactions.

To test mechanism (b) in Scheme 1.14, the KSIE for the reaction of 8 with 3-cyanopyridine at 25.0° was determined. This pyridine base was chosen because of its low value of q (and therefore a substantial KSIE should be observed if mechanism (b) were responsible for formation of ethenesulfonate anion (19)), and also because of its very low pK_a in water. When 8 was reacted with 3-cyanopyridine at apparent pH 4.0 and 25.0° in D_2O (containing 0.1 M potassium chloride), the observed pseudo first order rate constant ($k_\psi = 2.03 \times 10^{-2} s^{-1}$) gave a KSIE ($k_\psi(H_2O)/k_\psi(D_2O)$) of 0.97. This result is not consistent with the generation of the ethenesulfonate anion (19) by a general base catalysed hydrolysis mechanism (i.e. path (b) in Scheme 1.14).

Summary

The results presented thus far (which are summarized below) do not argue in favor of the separate mechanisms ((b) and (c)) for the formation of the products in the reactions of 8 and 12 with substituted pyridine bases.

a) The effect of the methyl substituent in 12 upon the second order rate constants is larger than can reasonably be accounted for on the basis of a direct attack at sulfonyl sulfur.

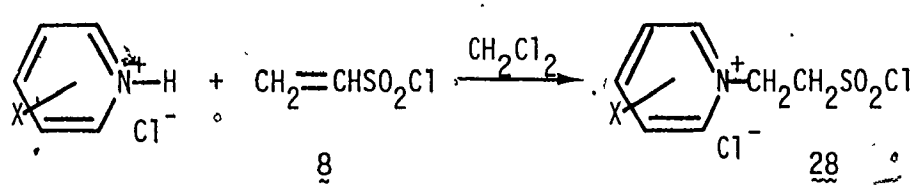
b) The Brönsted coefficient calculated for the nucleophilic catalysis mechanism at sulfonyl sulfur (from the partitioned rate constants k_S) is very different from the coefficient obtained for a well established mechanism of this type.

c) The observed KSIE for the reaction of 3-cyanopyridine with 8 is well below the range expected for a general base catalysed hydrolysis mechanism (21).

The suitability of the vinylogous nucleophilic catalysis mechanism (path (a) Scheme 1.13) for the generation of the reaction products is now examined.

(g) Reaction of N-[2-Chlorosulfonylethyl] pyridinium Chloride (28) with Pyridine in Water and Deuterium Oxide Containing 0.1 M Potassium Chloride at 25.0°C

The vinylogous nucleophilic catalysis mechanism presented earlier requires the formation of a pyridiniosulfene (16) intermediate. As an alternative means of generating the proposed sulfene (16) intermediate *in situ*, N-[2-Chlorosulfonylethyl]pyridinium chloride (28a) was prepared from 8 by a method originally discovered by Loosmore (57). The sulfonyl chloride (28a) gave satisfactory elemental analysis, and its ^1H n.m.r. (CD_3NO_2) and infrared spectra exhibited absorptions consistent with the assigned structure.

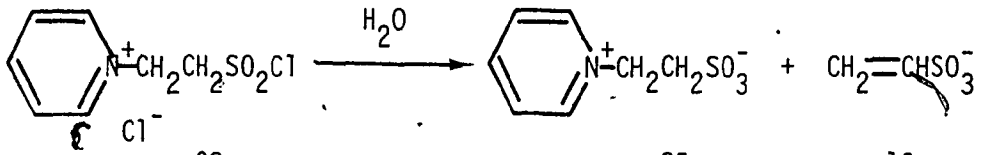


8 28

X = H, 28a

This compound was not very stable to further purification and was therefore used as isolated in the following solvolysis reactions.

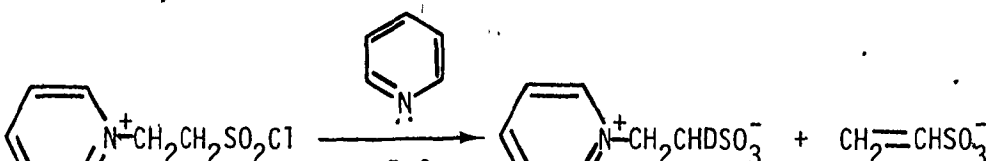
The sulfonyl chloride (28a) was hydrolysed in water and D_2O at pH 4.0 using the pH-stat apparatus. The reaction products were found to be the pyridine betaine (25a) and ethenesulfonate anion (19) in both reactions.



28a 25a 19

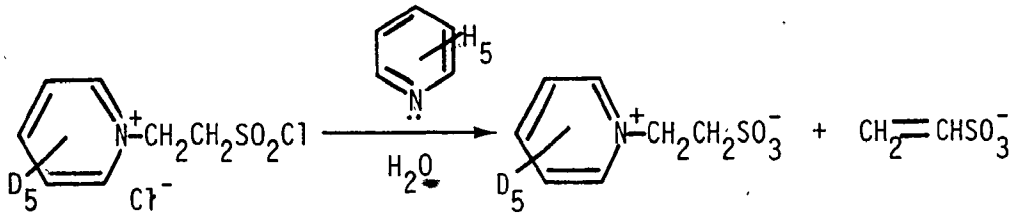
The betaine (25a) comprised 88% of the mixture for the reaction in water and 86% for the reaction performed in D_2O. For the reaction in D_2O, 25a was observed to be ~80% monodeuterated at the methylene α to the sulfonate group, but no deuterium was observed in 19.

The sulfonyl chloride (28a) was then reacted with a large excess of pyridine in water and D_2O at pH 4.0. Again the betaine (25a) and ethenesulfonate anion (19) were generated. For the reaction performed in water, 25a was formed in 83% relative yield. In D_2O 25a was produced in 76% yield, and was estimated (by ^1H n.m.r. integration) to be ≥95% monodeuterated at the carbon α to the sulfonate group. No deuterium was observed in the ethenesulfonate anion (19).



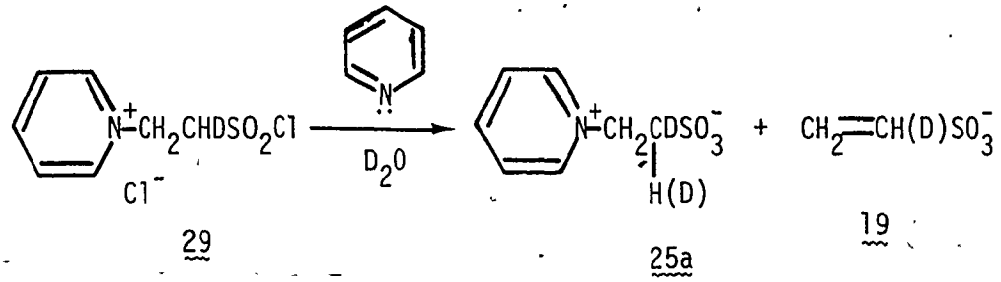
28a 25a 19

The possibility that the reaction of 28a with pyridine was proceeding through formation of 8 was eliminated by the following experiment. N-[2-chlorosulfonylethyl]pyridinium-d_5 chloride (28b) was prepared and reacted with natural abundance pyridine in water at pH 4.0 and 25.0°. The pyridine-d_5 betaine (25b) was generated in 81% relative yield, with 19 as the remaining product. There was no detectable protiated pyridine betaine (25a) in the ^1H n.m.r. spectrum of the crude product mixture.



28b 25b 19

Another possibility, namely that the pyridiniosulfonyl chloride (28a) was a reactive intermediate produced in the reaction of 8 with pyridine, was eliminated on the basis of the results of the reactions performed in D_2O. If 28a were an intermediate in this reaction then a substantial proportion of the isolated betaine (25a) would have been expected to have incorporated more than one deuterium in the α position, contrary to experimental results. To confirm this prediction, N-[2-chlorosulfonylethyl]-2-d pyridinium chloride (29) was prepared, and then reacted with pyridine in D_2O at apparent pH 4.0. The isolated betaine (25a) was found to have exchanged ~1.5 α hydrogen atoms, and the ethenesulfonate anion (19) was also observed to be substantially (≥40%) α monodeuterated.

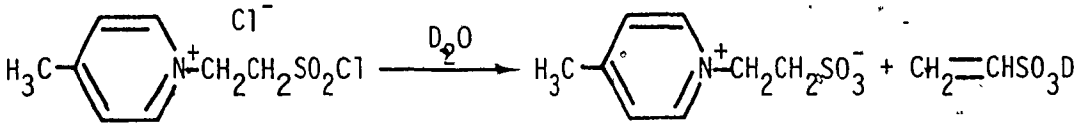


29 25a 19

(h) Reactions of N-4'-Methyl[2-Chlorosulfonylethyl]pyridinium Chloride (28c) with 4-Picoline in Water and Deuterium Oxide

To test whether substituted pyridiniosulfene (16) intermediates generated in situ would generate product ratios corresponding to the reaction of 8 with the substituted pyridine, N-4'-methyl[2-chlorosulfonylethyl]pyridinium chloride (28c) was prepared from 8 and solvolysed in the absence and presence of 4-picoline.

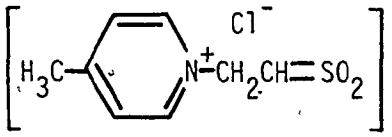
The sulfonyl chloride (28c) was solvolysed in D_2O at room temperature in an n.m.r. tube. After 1 hour the ^1H n.m.r. spectrum indicated the presence of 4-picoline betaine (25c) and ethenesulfonic acid. The betaine was estimated to comprise ≥95% of the relative proportion of the products. No deuterium was observed in either product.



28c 25c

The sulfonyl chloride (28c) was then reacted with excess 4-picoline at 25.0° and pH 4.0 in 0.1 M aqueous potassium chloride solution. The 4-picoline betaine (25c) and ethenesulfonate anion (19) were produced, with 25c comprising 92% of the mixture. The relative yield of 25c here compared very well with the corrected value of q determined for the

reaction of 8 with 4-picoline under similar reaction conditions (q = 0.88). The agreement in the product ratios for the reactions of 8 and 32 with 4-picoline is in support of a common 4'-methylpyridiniosulfene (16b) intermediate for these reactions.

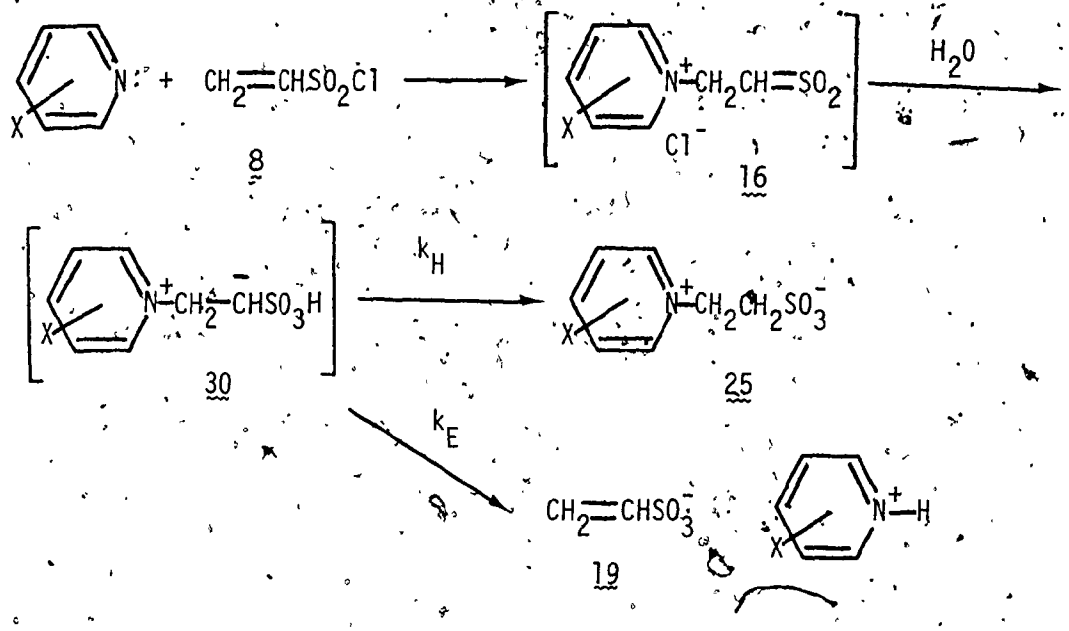


16b

The results of the product ratio experiments with the pyridiniosulfonyl chlorides (28a), (28b), (28c) and (29) argue strongly for the intermediacy of the pyridiniosulfene (16) intermediate in the reactions of ethenesulfonyl chloride (8) (and by extension, 12) with substituted pyridines in water. Therefore the generation of the alkenesulfonate products from the reactions of 8 and 12 with substituted pyridines in water is concluded to be proceeding via the vinylogous nucleophilic (S_N2') catalysis mechanism (path (a) Scheme 1.13). The proposed full mechanism for the reaction of 8 (and 12) with substituted pyridines in water is shown in Scheme 1.16. In this reaction the rate determining step for the formation of both of the observed products is the S_N2' attack of the substituted pyridine base upon 8 or 12 to generate the substituted pyridiniosulfene (16) intermediate. However, whether this step is a concerted displacement reaction or involves the irreversible formation of a carbanion intermediate prior to collapse to the sulfene (16), is a question (58) open to discussion.

The pyridiniosulfene (16) is then trapped by water to generate a zwitterion (30), which is then either protonated (denoted by k_H) to give the betaine (25) product or eliminates the substituted pyridine

SCHEME 1.16

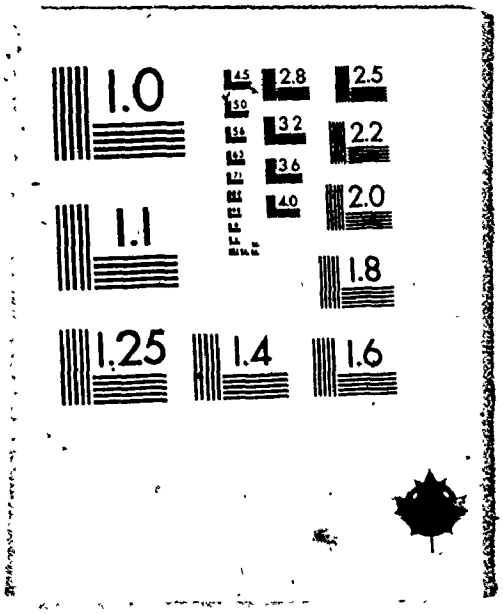


to give 19 (the rate constant for this process is represented by k_E). The nature of the substituent (X) present in the structure of the zwitterion (30) might be expected to perturb the relative ease of protonation versus elimination. In this respect the leaving group ability (nucleofugality) of the substituted pyridine could have a substantial effect upon the product ratios. Those pyridines with electron withdrawing substituents incorporated into the ring nucleus could enhance k_E relative to k_H from the zwitterion (30). This is nicely consistent with the observation of a lower yield of betaine product in the reactions performed with less basic substituted pyridines. The idea of a discrete zwitterion (30) intermediate is also consistent with the isotope effect of ~1.9* observed for the product ratio in the reaction of 8 with pyridine in water versus D_2O.

With the mechanism of the reaction of substituted pyridines with 8 and 12 in water now reasonably well established, the steric effects

*(See Section 1.2(d)).

2



of the hindered bases may be compared to those reported by King and Loqsmore (40) for the alcoholysis reactions of 8 in methylene chloride at -70°. While the difference in the rate constants for the alcoholyses of 8 catalysed by pyridine and 2,6-lutidine at -70° is approximately 10,000, in the present work at 25.0° this difference is only 560. Using the activation parameters determined for the reactions of 8 with pyridine and 2,6-lutidine in water, this rate difference corresponds to a hypothetical rate difference of approximately 750 in water at -70°. While these rate differences must be regarded as only very approximate values, they are nicely consistent with a large ground state solvation effect in water where the difference between the solvation energy of pyridine and 2,6-lutidine is greater than the corresponding difference in methylene chloride. Consequently, the $\Delta\Delta G^{\ddagger}$ for the reactions between 8 and pyridine versus 2,6-lutidine in water is smaller than the corresponding value in methylene chloride, leading to an apparently smaller steric effect in water.

(i) Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in Aqueous Mixtures of 1,2-Dimethyoxyethane Containing 0.1 M Potassium Chloride at 25.0°C

To determine the effect of a less polar medium than water upon the second order rate constants (k_B's), Brönsted β coefficients and steric effects for this reaction, a study of the hydrolysis reactions of 8 with substituted pyridines in aqueous mixtures of 1,2-dimethoxyethane (DME) was performed. This medium was chosen because the reactants and products were soluble, and because pH-stat kinetics in aqueous DME solvents had already been successfully performed in our own laboratory (59).

Solvent Polarity Determination for Aqueous Mixtures of 1,2-Dimethoxyethane at 25.0°C: Hydrolysis of 2-Chloro-2-Methylpropane in 0.1 M Potassium Chloride

Y-values were determined for 30% and 50% aqueous DME mixtures* using the method described by Winstein and Fainberg (60). The results of the hydrolyses of 2-chloro-2-methylpropane in these solvents are given in Table 1.22. As expected, 50% aqueous DME was observed to be the least polar of the solvents tested. The greatest change in solvent polarity occurred from water to 30% DME ($\Delta Y = 1.03$), with a smaller change in polarity ($\Delta Y = 0.83$) occurring from 30% to 50% DME.

TABLE 1.22

Determination of Y-values for Aqueous Mixtures of 1,2-Dimethoxyethane Containing 0.1 M Potassium Chloride: Observed Rate Constants for the Solvolysis of 2-Chloro-2-Methylpropane at pH 4.0 and 25.0°C

initial concentration of 2-chloro-2-methylpropane: 3×10^{-4} M

% DME	X_{H_2O} (a)	$10^3 \cdot k_\psi (s^{-1})$	Y (b)	ΔY
0	1.0	30.3	3.51 (c)	--
30	0.95	2.78	2.48	1.03
50	0.85	0.416	1.65	0.83

(a) mole fraction of water.

(b) as determined from: $mY = \log(k/k_0)$ where $m = 1$ and $k_0 = 9.26 \times 10^{-6} s^{-1}$ for 80% aqueous ethanol at 25.0°C (60).

(c) literature value of Y for H_2O is 3.493 at 25.0°C (60) in the absence of potassium chloride.

*30% DME containing 0.1 M potassium chloride was prepared volumetrically by adding DME (15 mL) to potassium chloride (0.400 g) in a flask (50 mL), and then filling to the mark with water. 50% DME was prepared in an analogous manner.

Hydrolysis of Ethenesulfonyl Chloride (8) in 30% and 50% Aqueous 1,2-Dimethoxyethane Containing 0.1 M Potassium Chloride at 25.0°C

The rates of the uncatalysed hydrolyses of ethenesulfonyl chloride (8) in 30% and 50% DME at 25.0° were determined at several different pH values in the manner previously described. The observed pseudo first order rate constants (k_ψ) for these reactions are given in Table 1.23.

The rates of the reactions of 8 with four unhindered and two hindered pyridine bases in these solvents at 25.0° were also examined. The observed pseudo first order rate constants (k_ψ) were obtained in the usual manner for three different concentrations of the free substituted pyridine base, and these results are given in Tables 1.24, 1.25. The first order plots were straight to ≥90% reaction (unless otherwise noted), indicating that the reactions obeyed first order kinetics under these conditions. From these results (taken with the mean values of the uncatalysed hydrolysis reactions of 8) plots of k_ψ versus free pyridine base were constructed for the reaction of each substituted base with 8 in 30% and 50% DME. These plots were all observed to be linear, indicating a first order dependence of the reaction upon the free base concentration. The second order rate constants for these reactions were obtained by least squares analysis of these plots, and the results of these plots are given in Table 1.26.

The products of the reaction between 8 and pyridine in 30% DME were investigated in the usual manner and found to consist of the pyridine betaine (25a) and ethenesulfonate anion (19) in 53% and 47% relative yields, respectively (corrected q = 0.53).

Using the data in Table 1.26 Brönsted plots of log k_B versus pK_a were constructed for the reactions in 30% and 50% DME. These plots are

TABLE 1.23

Observed Pseudo First Order Rate Constants for the Hydrolysis of Ethenesulfonyl Chloride (8) in Aqueous 1,2-Dimethoxyethane Containing 0.1 M Potassium Chloride at 25.0°C

30% DME

initial sulfonyl chloride concentration: 1.0×10^{-3} M

Apparent pH	$10^3 \cdot k_\psi (s^{-1})$
3.0	1.58
4.0	1.56
5.0	1.41
6.0	1.69[a]
	mean value = 1.56 ± 0.15[b]

50% DME

initial sulfonyl chloride concentration: 5×10^{-4} M

Apparent pH	$10^3 \cdot k_\psi (s^{-1})$
3.0	0.763
3.0	0.774
3.0	0.800
	mean value = 0.78 ± 0.02[b]
4.0	1.04
4.0	1.08
4.0	1.00
	mean value = 1.04 ± 0.04[b]
5.0	1.45
6.0	1.40
	mean value = 1.42 ± 0.02[b]

a) reaction followed to ≥80% reaction.
b) standard deviation.

TABLE 1.24

Observed Pseudo First Order Rate Constants for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 30% 1,2-Dimethoxyethane Containing 0.1 M Potassium Chloride at 25.0°C

average initial sulfonyl chloride concentration: 1×10^{-3} M

Pyridine	pK_a [a]	$10^4 \cdot$[Pyridine] (M) [b]	pH	$10^2 \cdot k_\psi (s^{-1})$
3,4-$(CH_3)_2$	5.95	0.99	4.0	2.36
		1.38	4.0	2.88
		1.98	4.0	3.82
4-CH_3	5.53	0.303	3.0	0.585
		0.606	3.0	1.05 [c]
		0.909	3.0	1.50
H	4.88	1.62	3.0	1.48
		2.43	3.0	2.34
		3.23	3.0	2.79
3-$NHCOCH_3$	3.98	5.23	3.0	2.79
		6.97	3.0	3.55
		8.36	3.0	3.87
2-CH_3	5.50	3.13	4.0	0.627
		6.26	4.0	0.944
		9.39	4.0	1.47
2,6-$(CH_3)_2$	6.16	150	7.0	0.336 [d]
		300	7.0	0.506 [d]
		450	7.0	0.716

a) determined from titration curve in 30% DME.
b) free pyridine base concentration.
c) straight to 80% reaction.
d) followed to 90% reaction.

TABLE 1.25

Observed Pseudo First Order Rate Constants for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 50% 1,2-Dimethoxyethane Containing 0.1 M Potassium Chloride at 25.0°C

average initial sulfonyl chloride concentration: 5×10^{-4} M

Pyridine	pK_a[a]	$10^4 \cdot$[Pyridine] (M)[b]	pH	$10^2 \cdot k_\psi$ (s^{-1})
3,4-$(CH_3)_2$	5.44	0.191	3.0	0.671
		0.319	3.0	1.03
		0.637	3.0	1.71[c]
4-CH_3	5.07	0.430	3.0	0.753[d]
		0.861	3.0	1.68
		1.29	3.0	2.22
H	4.52	2.16	3.0	2.34[c]
		3.61	3.0	3.55
		4.34	3.0	4.17
2-$NHCOCH_3$	3.78	3.43	3.0	2.05
		7.24	3.0	4.29
		9.31	2.6	4.84
2-CH_3	5.10	8.90	4.0	1.85
		14.9	4.0	2.64
		22.3	4.0	3.54
2,6-$(CH_3)_2$	5.65	163	7.0	0.362
		488	7.0	0.770
		814	7.0	1.16

a) determined from titration curve in 50% DME.
b) free pyridine base concentration.
c) straight to 80% reaction.
d) followed to 80% reaction.

TABLE 1.26

Second Order Rate Constants for the Reactions of Ethenesulfonyl Chloride (8) with Substituted Pyridines in Aqueous Mixtures of 1,2-Dimethoxyethane Containing 0.1 M Potassium Chloride at 25.0°C

30% DME

Pyridine	pK_a	k_B ($M^{-1}s^{-1}$)	r	log k_B
3,4-$(CH_3)_2$	5.95	186	0.994	2.27
4-CH_3	5.53	149	0.999	2.17
H	4.88	84	0.997	1.92
3-$NHCOCH_3$	3.98	46	0.995	1.66
2-CH_3	5.50	14	0.996	1.15
2,6-$(CH_3)_2$	6.16	0.12	0.999	-0.92

50% DME

Pyridine	pK_a	k_B ($M^{-1}s^{-1}$)	r	log k_B
3,4-$(CH_3)_2$	5.44	254	0.995	2.40
4-CH_3	5.07	171	0.995	2.23
H	4.52	94	0.998	1.97
3-$NHCOCH_3$	3.78	53	0.994	1.72
2-CH_3	5.10	15	0.992	1.18
2,6-$(CH_3)_2$	5.65	0.12	0.999	-0.92

illustrated in Figures 1.9, 1.10. Again the unhindered pyridines described a linear relationship. For 30% DME the equation of the line was $\log k_B = 0.32\ (pK_a) + 0.37$ with $r = 0.999$, and for 50% DME, $\log k_B = 0.41\ (pK_a) + 0.14$ with $r = 0.997$. The hindered pyridine bases were considerably off these lines and the magnitudes of their deviations are given in Table 1.27. The overall behavior of 8 towards substituted pyridines in these solvents is similar to that observed in water at 25.0°. Presumably then, the mechanism of formation of the observed products in aqueous DME solvents has remained unchanged from the mechanism proposed in water, although this has not been rigorously established. Therefore the results of the rate measurements for the reaction between 8 and substituted pyridines in water and aqueous DME solvents may be compared within the framework of a common mechanism.

From the results presented in Table 1.27 it is apparent that the steric effects in 30% and 50% DME are not significantly greater than those obtained in water at 25.0°. However, the second order rate constants for all of the pyridine bases are larger in aqueous DME than in water, with the effect being most pronounced for the most nucleophilic pyridine base (3,4-lutidine). This observation, along with the irregular changes in the values of β as the solvent composition is altered, may be more easily understood if we consider the possibility of a pre-equilibrium between the independently solvated neutral reagents and a solvated complex of the sulfonyl chloride 8 with the pyridine base (represented by K_1), as shown in Scheme 1.17.

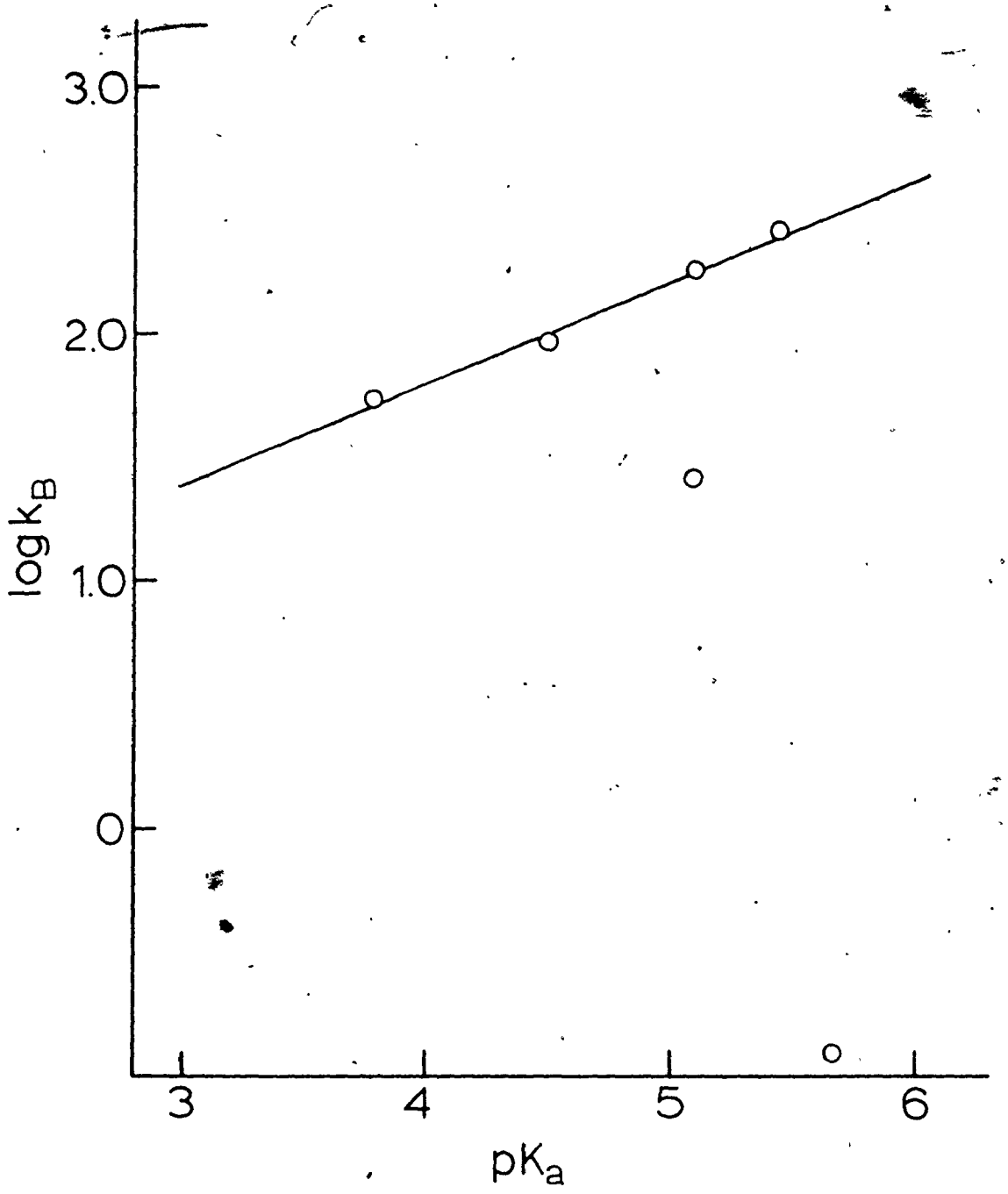


FIGURE 1.9

Brönsted Plot for Reaction of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 30% DME at 25.0°C

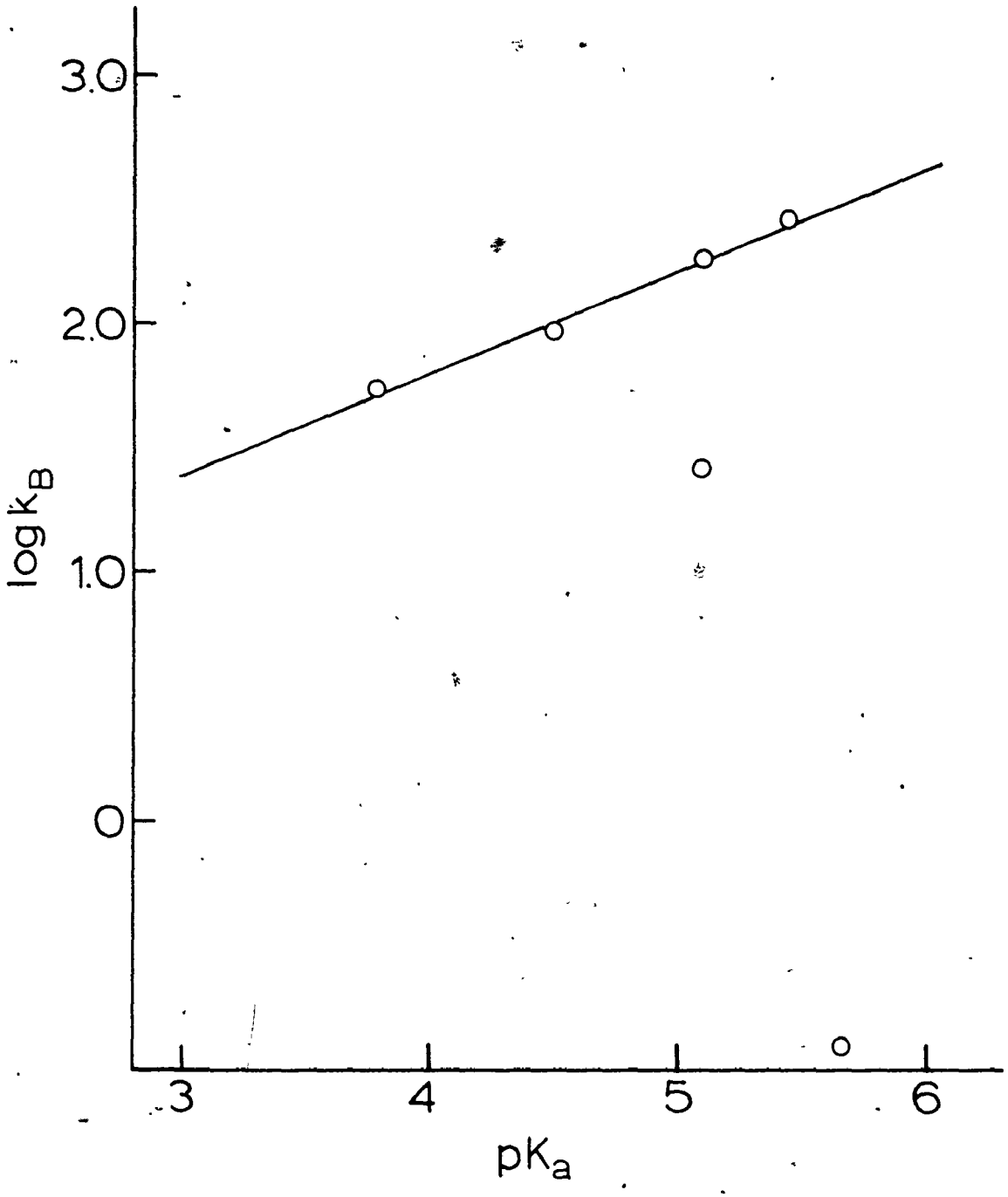


FIGURE 1.10

Brönsted Plot for Reaction of Ethenesulfonyl Chloride (8) with Substituted Pyridines in 50% DME at 25.0°C

TABLE 1.27

Deviations in the Brönsted Plots for the Reactions of Hindered Pyridines with Ethenesulfonyl Chloride (8) in Aqueous Mixtures of 1,2-Dimethoxyethane at 25.0°C

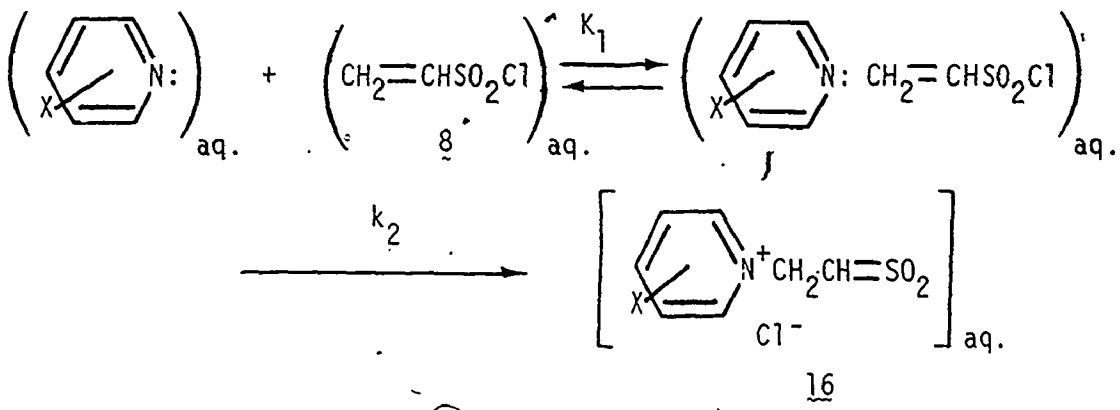
Pyridine	Solvent	log k_B	$\Delta(M^{-1}s^{-1})$	$\frac{k_B(\text{pyridine})}{k_B(\text{subst. pyridine})}$
2-CH_3	water[a]	0.84	8.1	4.1
2,6-$(CH_3)_2$	water	-1.31	2.1×10^3	5.6×10^2
2-CH_3	30% DME[b]	1.15	10	6.3
2,6-$(CH_3)_2$	30% DME	-0.92	1.9×10^3	7.3×10^2
2-CH_3	50% DME[c]	1.18	11	6.3
2,6-$(CH_3)_2$	50% DME	-0.92	2.4×10^3	7.7×10^2

a) For water: $\log k_B = 0.32\ (pK_a) - 0.22$

b) For 30% DME: $\log k_B = 0.32\ (pK_a) + 0.37$

c) For 50% DME: $\log k_B = 0.41\ (pK_a) + 0.14$

SCHEME 1.17



16

The formation of the pyridiniosulfene (16) from the solvated complex would then be the rate determining step (represented by k_2) of the reaction*.

The increasing magnitudes of the second order rate constants (k_B's) for these reactions in a less polar medium suggests that the free energies of the reactants may be more affected by the change in solvent composition than the transition state (61). It is also not unreasonable to expect that the position of the pre-equilibrium will be largely affected by the extent of hydrogen bonding by the solvent to the pyridine base (62,63). If we may also consider the observed β value for the reaction to be a composite** of (at least) two separate β values, then a combination of these values for the pre-equilibrium association (where β is presumably negative) and the rate determining step (β is

---

* i.e. $k_B = k_2 \cdot K_1$ where K_1 is the equilibrium constant for the pre-equilibrium and k_B is the observed second order rate constant.

** If $k_B = k_2 \cdot K_1$
then $\log(k_B) = \beta \cdot pK_a + C = \log k_2 + \log K_1$

$\therefore \log k_2 = \beta_2 \cdot pK_a + C_2$
$\log K_1 = \beta_1 \cdot pK_a + C_1$

where $\beta_1 + \beta_2 = \beta$ and $C_1 + C_2 = C$

positive) could result in the observed β value and also explain the increased reactivity of the unhindered pyridines in the less polar solvent. This is qualitatively illustrated in Figure 1.11.

Although this approach is qualitative and may well be incomplete, it does point out that it may be prudent to consider the possibility that an observed Brönsted β value may be a composite of several β values representing discrete steps along a reaction coordinate up to the rate determining step. This consideration reinforces the recent statements by authors who urge caution in the use of observed Brönsted β values in the interpretation of transition state structure (64).

The slight increase in the magnitude of the ratio of k_B(pyridine)/ k_B(2,6-lutidine) in the less polar solvents could be the result of a slight decrease in the ground state solvation energy of pyridine relative to 2,6-lutidine in the less polar protic solvents.

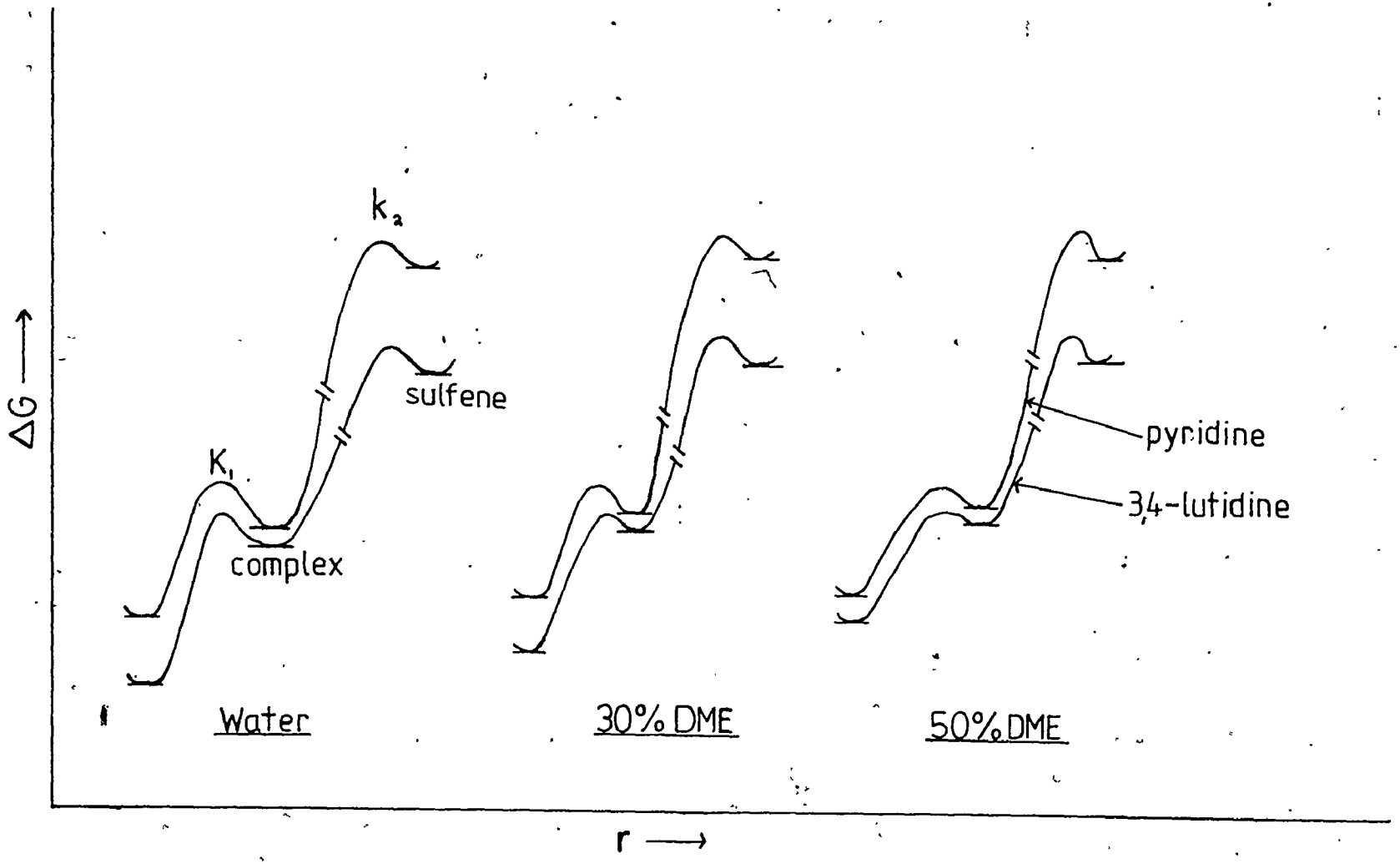


FIGURE 1.11 Energy Diagram for Reaction of Ethenesulfonyl Chloride (8) with Substituted Pyridines in Aqueous 1,2-Dimethoxyethane Solvent Mixtures

1.3 Conclusions

For the hydrolyses of ethenesulfonyl chloride (8) and trans-1-propene-1-sulfonyl chloride (12) in the absence of pyridine bases, the mechanism is concluded to be predominantly conventional S_N2 nucleophilic attack of water at sulfonyl sulfur. However, a small amount of S_N2' attack of water to generate hydroxymethylsulfene (24) is probably occurring in the hydrolysis of ethenesulfonyl chloride (8) to yield isethionate (20).

For the reaction performed in water in the presence of substituted pyridine bases, the mechanism by which the betaine and alkenesulfonate products are generated is concluded to be proceeding via formation of a pyridiniosulfene (16) intermediate, followed by formation of a zwitterion (30) intermediate. Therefore, the generation of the alkenesulfonate anion from the alkenesulfonyl chloride in these reactions is an example of vinylogous nucleophilic catalysis.

When aqueous mixtures of 1,2-dimethoxyethane were employed as the reaction medium for these reactions, these solvents produced only minor effects on the kinetics and product ratio compared with the reactions performed in water.

The results of this chapter are in harmony with those of King and Loosmore (40) (which were performed in methylene chloride at -70°), and therefore substantiate the claim for the previously unreported vinylogous nucleophilic catalysis mechanism for the pyridine catalysed hydrolysis and alcoholysis reactions of ethenesulfonyl chloride (8) and trans-1-propene-1-sulfonyl chloride (12).

1.4 Experimental

Elemental analyses were performed by Microanalysis Laboratories Ltd., formerly of Toronto and Thornhill, Ontario, now located in Markham, Ontario. Deuterium analyses were performed by J. Nemeth, Urbana, Illinois, U.S.A. Nuclear magnetic resonance spectra (n.m.r.) were recorded using Varian T-60, HA-100 and XL-100 spectrometers. Spectra recorded in deuterochloroform (Merck, Sharp and Dohme Ltd.) and nitromethane-$\underline{d}_3$ (Aldrich, 99 atom%D) were calibrated with tetramethylsilane (TMS, Merck, Sharp and Dohme). Spectra recorded in deuterium oxide (D_2O, Merck, Sharp and Dohme) were calibrated either with sodium 3-(trimethylsilyl) propionate (TSP, Aldrich) or sodium 3-(trimethylsilyl)propanesulfonate (DSS, Aldrich). All δ values ~~reported~~ were recorded from spectra obtained on XL-100 or HA-100 spectrometers, unless otherwise stated.

Infrared (i.r.) spectra were recorded on Perkin-Elmer 621 or Beckman 4250 spectrometers using sodium chloride or potassium bromide optics. All i.r. spectra were calibrated with a polystyrene reference film. All melting points were obtained on a Gallenkamp melting point apparatus, and are uncorrected. All temperatures reported are in degrees Celsius. Refractive indices were determined on a thermostatically controlled Bausch and Lomb Abbe refractometer. The cold finger distillation apparatus used in micro-distillation has been previously described (65).

1,2-Dimethoxyethane (Eastman) and methylene chloride (Fisher) were dried by distillation from calcium hydride (Fisher) and stored over molecular sieves (3 Å grade 564, 8-12 mesh). All other solvents used were reagent grade (Fisher) unless otherwise specified. Rexyn 300

(HOH) (Fisher) was used as supplied, usually in excess. Standard sodium hydroxide and hydrochloric acid solutions were prepared volumetrically from sodium hydroxide solution concentrate, N/1 or N/10 (Fisher). For a few kinetic determinations the titrant used was prepared from sodium hydroxide electrolytic pellets (Fisher); identical rate constants were obtained from titrant solutions prepared by either method.

The spinning band distillation apparatus was equipped with a 24" Teflon spinning band. The complete unit was a Nester/Faust model NFT50 (Nester/Faust Manufacturing Corp., Newark, Delaware).

Methylene chloride and ether extracts were dried over anhydrous magnesium sulfate (Fisher, certified grade) prior to evaporation.

Picric acid (Fisher), potassium chloride (Fisher), dimethyl sulfate (BDH), 20% DCl/D_2O solution (Sigma, 98 atom%D) were used as supplied. Sodium metal (BDH) was stored under paraffin oil. Sodium 2-hydroxyethanesulfonate (sodium isethionate) (Eastman) was used as supplied; ^1H n.m.r. (D_2O) δ: 3.12 (t, 2H), 3.90 (t, 2H).

The apparatus used for the kinetic determinations consisted of a Radiometer Model 25 pH meter equipped with a Radiometer Titrator 11 automatic titrator, a Radiometer GK2401B glass electrode and an Aminco automatic buret with a 3 mL syringe reservoir. The reaction vessel employed was a Radiometer V520 vessel equipped with a V525 thermostatting jacket. The temperature was maintained constant ($\pm 0.1^{\circ}$) by means of a Haake FJ constant temperature circulating apparatus. Stirring was accomplished by the use of a magnetic stirrer. Time was measured with a Precision Scientific Co. electric timer.

Preparation of Ethenesulfonyl Chloride (8)

Ethenesulfonyl chloride (8) was prepared from 2-chloroethanesulfonyl chloride; both were prepared by the method of Le Berre et al (39). Ethenesulfonyl chloride (8) was further purified by fractional distillation under reduced pressure (1.5 mm Hg, b.p. 25°) using the spinning band apparatus. ^{1}H n.m.r. ($CDCl_3$) δ: 6.2 - 7.2 (ABC multiplet, 3H; 7.06 (CH), 6.17 (H trans to CO_2Cl), 6.53 (H cis to SO_2Cl); J_{AB} = 9.5 Hz, J_{AC} = 16.5 Hz, J_{BC} = 1.5 Hz); i.r. (CH_2Cl_2) 3116 (w), 3074 (m), 1380 (vs), 1170 (vs), 982 (s), 941 (m), 650 (s) cm^{-1}; n_D^{20} 1.4681 (lit (66), n_D^{20} 1.4686).

Preparation of 2-Chloropropane-1-sulfonyl Chloride

2-Chloropropane-1-sulfonyl chloride was prepared by the method of Stewart and Cordts (67) from sodium 2-hydroxypropane-1-sulfonate (prepared by reaction of propylene oxide (Fisher with sodium metabisulfite (Fisher)) and phosophorus pentachloride (Fisher). The crude product was obtained by distillation under reduced pressure (5.0 mm, b.p. 30 - 55°). The distillate was used without further purification in the preparation of trans-1-propene-1-sulfonyl chloride (12).

Preparation of trans-1-Propene-1-sulfonyl Chloride (12)

Trans-1-propene-1-sulfonyl Chloride (12) was prepared by the method of Harding (68) from 2-chloropropane-1-sulfonyl chloride. The ^{1}H n.m.r. ($CDCl_3$) spectrum of the crude material had the following absorptions: A_3XY pattern, 5H; δ_A 2.02 (d of d, 3H), δ_X 6.77 (H cis to SO_2Cl, d of q), δ_Y 7.15 (q of d, 1H); J_{XY} = 14.5 Hz, J_{AX} = 6.5 Hz, J_{AY} = 1.5 Hz. This pattern

was attributed to the trans isomer (relative proportion approximately 95% of the crude mixture): another A_3XY pattern, 5H; δ_A 2.31 (m, 3H), δ_X 5.95 (m, 1H), δ_Y 6.32 (m, 1H); J_{XY} = 2 Hz (attributed to 1-propene-2-sulfonyl chloride). A pure specimen of the trans isomer was obtained by a reduced pressure spinning band distillation (15 mm, b.p. ~70°), i.r. (CH_2Cl_2) 3062 (w), 1686 (m), 1439 (m), 1375 (vs), 1298 (w), 1174 (s), 945 (s), 808 (s) cm^{-1}.

Characterization of Ethenesulfonate Anion (19)

Ethenesulfonyl chloride (8) (0.20 g, 1.57×10^{-3} mol) was hydrolysed at pH 4.0 in 0.1 M potassium chloride at room temperature. After 2 hours the solvent was evaporated, and the residue dissolved in hot water (5 mL). To this solution, a solution of S-benzylthiuronium chloride (0.32 g, 1.57×10^{-3} mol), (prepared from benzyl chloride and thiourea by the method of Donleavy (69)) in water (5 mL) was added. After cooling to room temperature, the crystalline precipitate was removed by filtration and recrystallization from 95% alcohol (m.p. 145 - 146.5°, lit. m.p. 145 - 146° (70)).

Preparation of 3-Ethanamidopyridine

3-Ethanamidopyridine was prepared by reacting 3-aminopyridine (prepared (71) from nicotinamide with sodium hypobromite) with acetic anhydride according to the method of Camps (71). The crude product (m.p. 128 - 130°) was recrystallized from benzene (m.p. 133 - 134.5°, lit. m.p. 133° (71)).

Preparation of 3-Cyanopyridine

3-Cyanopyridine was prepared from the reaction of nicotinamide with phosphorus pentoxide according to the method of La Forge (72). The product was obtained by means of a vacuum distillation (30 mm Hg), m.p. 49.5 - 51° (lit. m.p. 50 - 51° (72)). The product was used without further purification.

Other Substituted Pyridine Bases

3,4-Dimethylpyridine (3,4-lutidine, Aldrich), 3,5-dimethylpyridine (3,5-lutidine, Aldrich), 4-methylpyridine (4-picoline, Eastman), 4-ethylpyridine (Eastman), 3-methylpyridine (3-picoline, Aldrich), methyl 4-pyridinecarboxylate (methyl isonicotinate, Aldrich), pyridine (Eastman) were all fractionally distilled at atmospheric pressure before use. 3-Carbamoylpyridine (nicotinamide, Sigma) was recrystallized from benzene (m.p. 128 - 129°, lit. m.p. 128° (73)). 2-Ethylpyridine (Aldrich) was purified by recrystallization of its picrate salt (prepared by the method of Brown and Murphey (74)) from 95% alcohol (m.p. 108.5 - 110°, lit. m.p. 107 - 108° (74)). The free base was then recovered by continuous extraction of an aqueous alkaline solution of the picrate salt with ether for 24 hours. The recovered free base was then fractionally distilled (b.p. 148 - 149° at atmospheric pressure). 2-Methylpyridine (2-picoline, Eastman) was purified in a similar manner by recrystallization of its picrate salt (prepared by the method of Bratton and Bailey (75)), m.p. 166 - 167°, lit. m.p. 166.5°(75). The free base was extracted from an alkaline aqueous solution of the picrate, and distilled at atmospheric pressure. Benzo[b]pyridine (quinoline, Eastman) was also purified through preparation of its picrate salt (prepared and purified

by the method of Bratton (75), m.p. 205 - 206°, lit. m.p. 203 - 203.5° (75)). The free base was recovered and distilled in an analogous manner. 2,6-Dimethylpyridine (Eastman) and 2,4,6-trimethylpyridine (Eastman) were treated with 5 mole % dimethylsulfate overnight, filtered and fractionally distilled at atmospheric pressure.

The purity of the hindered pyridines was established by performing a reaction with the base and ethenesulfonyl chloride (8), using initial sulfonyl chloride concentrations at or near those employed in the kinetic runs. The ^{1}H n.m.r. spectra of the crude reaction products (occasionally the crude products were treated with Rexyn 300 (HOH) deionizing resin to remove all ions except the betaine) was then compared with ^{1}H n.m.r. spectra of authentic samples of the pyridine betaines. The purity of the base was deemed acceptable when no absorptions due to betaines (other than the one corresponding to the pyridine employed) were observed in the ^{1}H n.m.r. spectrum.

Preparation of Substituted Pyridine Betaines of Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12)

The substituted pyridine betaines of 8 and 12 were prepared according to the method of Le Berre et al (39) in glacial acetic acid. For the reactions of 8 and substituted pyridines, the reactions were worked up after 2 - 3 hours at room temperature. The last traces of acetic acid were removed by azeotroping with toluene. The residue was recrystallized from 95% alcohol unless otherwise specified. The yields of the betaines (25) obtained in this manner were in the range 50 - 90%, depending upon the nucleophilicity of the base employed (hindered pyridines generally gave lower yields, sometimes <50%). For the reaction with 12, the reactions were usually allowed to stand at room

temperature overnight before workup. The reactions were worked up as before, and the residues recrystallized from 95% alcohol. The physical properties of these compounds are given in Tables 1.28, 1.29.

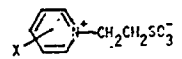
General Procedure for Determining the Uncatalysed Solvolysis Reaction Products for Ethenesulfonyl Chloride (8) and trans-1-Propene-1-sulfonyl Chloride (12) at 25.0°

The reaction products of the uncatalysed solvolysis reactions of 8 and 12 were determined at various pH values at 25.0°. A solution of the sulfonyl chloride in ~0.5 mL DME (the initial concentration of the sulfonyl chloride in these reactions was in the range 1.6×10^{-3} - 2.9×10^{-2} M) was injected into a stirred solution of potassium chloride in water or D_2O at 25.0° at the desired pH. The pH was maintained until the addition of titrant had stopped. For those reactions performed above pH 7, the reaction was then neutralized to pH 7 with dilute HCl solution. The solvent was then evaporated to dryness, and the residue investigated by ^1H n.m.r. spectroscopy. Integration of the peaks corresponding to the methylene protons of 20 and the characteristic vinyl protons of the alkenesulfonate anion (the peaks for both products were always well separated in the ^1H n.m.r. spectrum (D_2O)) gave the relative proportions of the observed products. The results of these experiments are given in Table 1.5.

Products of the Reaction of Ethenesulfonyl Chloride (8) with Pyridine in Water Containing 0.1 M Potassium Chloride at 25.0°

Ethenesulfonyl chloride (8) (0.065 g, 5.2×10^{-4} mol) was allowed to react with a solution of pyridine (1.0 mL, 1.25×10^{-2} mol) in water (50 mL) containing potassium chloride (0.400 g, 5.36×10^{-3} mol)

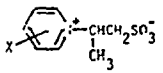
TABLE 1.28 Characterization of N-Pyridinium 2-Ethanesulfonates (25)



X	m.p. (°C)	analysis	i.r. (ν_{max} cm^{-1}, nujol)	^{1}H n.m.r. (D_2O) δ:
3,5-$(CH_3)_2$	315 - 316	Calcd. for $C_9H_{13}NO_3S$: C, 50.21; H, 6.09; N, 6.51; S, 14.89 Found: C, 50.13; H, 6.20; N, 6.38; S, 14.67	3045(m), 1641(m), 1515(m), 1488(m), 1272(m), 1251(s), 1210 (vs), 1183(vs), 1153(s), 1052(s), 1035(vs), 665(m)	2.49(s,3H), 2.61s,3H), 3.59(t,2H), 4.94(t,2H), 7.85(s,1H), 8.61(d,2H)
3,5-$(CH_3)_2$	370	Calcd. for $C_9H_{13}NO_3S$: C, 50.21; H, 6.09; N, 6.51; S, 14.89 Found: C, 50.28; H, 6.20; N, 6.42; S, 14.76	3062(m), 1600(m), 1263(m), 1210(vs), 1183(s), 1158(m), 1045(m), 1035(m), 687(m), 663(m)	2.46(s,6H), 3.55(t,2H), 4.90(t,2H), 8.22(s,1H), 8.52(s,2H)
4-CH_3	322 - 4	Calcd. for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51, N, 6.96, S, 15.93 Found: C, 47.91; H, 5.67; N, 6 78; S, 16.02	1645(m), 1488(m), 1208(vs), 1179(vs), 1034(s), 843(m)	2.68(s,3H), 3.59(t,2H), 4.86(t,2H), 7.92(d,2H), 8.76(d,2H)
4-C_2H_5	350 - 352 (decomp.)	Calcd. for $C_9H_{13}NO_3S$: C, 50.21; H, 6.09; N, 6.51; S, 14.89 Found: C, 50 45, H, 6.14, N, 6.41; S, 14.92	1642(m), 1515(w), 1205(vs), 1182(vs), 1031(s), 860(s), 730(s)	1.32(t,3H), 2.98(q,2H), 3.59(t,2H), 4.97(t,2H), 7.96(d,2H), 8.77(d,2H)
3-CH_3	279 - 280	Calcd. for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51, N, 6.96, S, 15.93 Found: C, 47.63; H, 5 57, N, 6.81; S, 15 79	3063(m), 1508(m), 1267(m), 1204(vs), 1171(s), 1050(s), 1034(s), 683(m), 663(m), 630(s)	2.50(s,3H), 3.52(t,2H), 5.00(t,2H), 7.98(t,1H), 8.25(d,1H), 8.78(m,1H)
3-$CONH_2$	303 - 304 (decomp.)	Calcd. for $C_8H_{10}N_2O_4S$. C, 41.73; H, 4.38; N, 12.17; S, 13.93 Found: C, 41.59; H, 4.51; N, 12.01; S, 13.76	3510(m), 3155(m), 3080(m), 3065(m), 1697(s), 1623(m), 1410(s), 1260(s), 1240(s), 1230(s), 1040(s), 1027(m), 740(m)	3.72(t,2H), 5.20(t,2H), 8.34(m,2H), 9.0-9.35(m,3H), 9.50(s,1H)
3-$NHCOCH_3$	291 - 292	Calcd. for $C_9H_{12}N_2O_4S$. C, 46.56; H, 5.21; N, 12.07; S, 13.81 Found: C, 46.41, H, 5.13; N, 11.78, S, 13.59	3401(w), 3226(w), 1515(m), 1212(s), 1171(s), 1042(s), 739(m), 726(m)	3.55(t,2H), 4.76(s,3H), 4.83(t,2H), 7.71(m,2H), 8.16(m,2H)
3-Cl	300 - 303 (decomp.)	Calcd. for $C_8H_8ClNO_3S$: C, 45.27; H, 3.80, N, 13.20, S, 15.10 Found: C, 45.21; H, 3.96; N, 13.06, S, 15 01	1632(w), 1495(m), 1273(m), 1220(vs), 1205(vs), 1175(s), 1150(m), 1057(m), 1043(s), 630(s)	3.68(t,2H), 5.20(t,2H), 8.38(t,1H), 9.05(m,3H), 9.35(m,1H), 9.62(m,1H)
3-CO_2CH_3	255 - 257	Calcd. for $C_9H_{11}NO_5S$: C, 44.08, H, 4.52; N, 5.71; S, 13 07 Found: C, 44 10, H, 4.60, N, 5.65, S, 12.89	3060(s), 1710(s), 1305(vs), 1280(s), 1120(vs), 1110(s), 1030(vs), 720(s), 635(s)	3.64(t,2H), 4.07(s,3H), 5.12(t,2H), 8.56(d,2H), 9.16(d,2H)
2-CH_2CH_3	254 - 256 (decomp.)	Calcd. for $C_9H_{13}NO_3S$ C, 50.21; H, 6.09; N, 6.51; S, 14.89 Found: C, 50.07; H, 6.17, N, 6.37, S, 14 63	3090(m), 3060(m), 1630(s), 1580(m), 1515(s), 1755(vs),1200 (vs), 1152(vs), 1048(vs), 1033(vs), 795(m), 781(m), 630(s)	1.44(t,3H), 3.24(q,2H), 3.56(t,2H), 5.01(t,2H), 7.99(m,2H), 8.52(t,1H), 8.85(d,1H)
$^2H_5$	256 - 258	Calcd. for $C_7{}^1H_4{}^2H_5NO_3S$: 55.56% excess ^2H Found: 53.50% excess ^2H		3.64(t,2H), 5.07(t,2H)
$^3H_5$ (b)	255 - 256			3.62(t,2H), 5.05(t,2H), 8.11(t,2H), 8.62(t,1H), 8.97 (d,2H)
2,6-$(CH_3)_2$	decomp. >340	Calcd. for $C_9H_{13}NO_3S$: C, 50.21; H, 6.09, N, 6.51; S, 14.89 Found: C, 50.11; H, 5.92, N, 6.46; S, 14.71	1620(m), 1583(m), 1495(m), 1250(m), 1213(s), 1175 (s), 1035(s), 823(m), 725(m)	2.66(s,6H), 3.50(m,2H), 4.92(m,2H), 7.78(d,2H), 8.25 (t,1H)
Benzo[b]-(2,3)	285 - 286			3.70(t,2H), 5.50(t,2H), 8.90-9.52(m,5H), 9.16(d,1H), 9.36(d,1H)
2,4,6-$(CH_3)_3$	m.p. decomp. >335	Calcd. for $C_{10}H_{15}NO_3S$: C, 52.28; H, 6.59; N, 6.11; S, 13.98 Found: C, 52.21; H, 6.63; N, 6.21; S, 13.68	1640(m), 1575(w), 1303(m), 1265(s), 1198(b,vs), 1140 (s), 1033(s), 1023(s), 745(m)	2.52(s,3H), 2.86(s,6H), 3.47(m,2H), 4.84(m,2H), 7.62 (s,2H)

(a) i.e. deuteroform.
(b) reference (39)

TABLE 1.29 Characterization of N-Pyridinium 2-Propanesulfonates (26)



X	m.p. (°C)	analysis	i.r. (ν_{max} cm^{-1}, nujol)	^{1}H n.m.r. (D_2O) δ:
3,5-$(CH_3)_2$	288 (subl.)	Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11; S, 13.93 Found: C, 52.53; H, 6.55, N, 6.04; S, 13 77	1600(m), 1511(m), 1230(vs), 1208(vs), 1183(vs), 1166(vs), 1145(s), 1035(vs), 1000(m), 878(m)	1.76(d,3H), 2.46(s,3H), 2.57(s,3H), 3.59(m,2H), 5.16 (m,1H), 7.85(d,1H), 8.65(m,2H)
3,5-$(CH_3)_2$	344 - 345 (decomp.)	Calcd. for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59, N, 6.11; S, 13 98 Found: C, 52.53; H, 6.65; N, 5.99, S, 13 77	1508(m), 1274(m), 1220(vs), 1182(vs), 1130(m), 1040(s), 895(m), 773(m), 695(m)	1.82(d,3H), 2.55(s,6H), 3.62(m,2H), 5.16(m,1H), 8.24 (s,1H), 8.65(s,2H)
4-CH_3	293 - 294 (decomp.)	Calcd. for $C_9H_{13}NO_3S$: C, 50.21, H, 6.09; N, 6.51; S, 14.89 Found: C, 50.01; H, 6.09; N, 6.62; S, 14.63	1647(s), 1272(s), 1202(vs), 1161(vs), 1070(m), 1031(s), 838(m), 772(s), 829(m)	1.80(d,3H), 2.69(s,3H), 3.62(m,2H), 5.22(m,1H), 8.04 (d,2H), 8.91(d,2H)
"	307 - 308	Calcd. for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51; N, 6.96; S, 15.93 Found C, 47 97, H, 5.44, N, 6.83, S, 15.88	1637(m), 1495(s), 1264(m), 1205(s), 1183(s), 1163(s), 1122(m), 1036(s), 797(m)	1.86(d,3H), 3.66(m,2H), 5.21(m,2H), 8.16(t,2H), 8.54 (t,1H), 9.05(d,2H)
3-CO_2CH_3	268 - 269 (decomp.)	Calcd for $C_{10}H_{13}NO_5S$: C, 46.32, H, 5.05, N, 5.40; S, 12.37 Found: C, 46.21, H, 5.15; N, 5.36; S, 12.31	1739(s), 1642(m), 1633(m), 1259(vs), 1264(s), 1235(vs), 1212 (vs), 1202(vs), 1172(vs), 1122(s), 1093(vs), 781(m), 773(m)	1.84(d,3H), 3.66(m,2H), 4.08(s,3H), 5.39(m,1H), 8.58 (d,2H), 9.12(d,2H)
3-CN	268 - 9 (decomp.)	Calcd. for $C_9H_{10}N_2O_3S$ C, 47.78; H, 4.46, N, 12.38; S, 14.17 Found. C, 47 50, H, 4.60, N, 12.19, S, 13.95	1639(w), 1499(m), 1261(m), 1224(s), 1198(s), 1170(s), 1156 (w), 1036(s), 783(m)	1.84(d,3H), 3.65(m,2H), 5.41(m,1H), 8.34(t,2H), 9.01 (d,1H), 9.32(d,1H), 9.67(s,1H)
2-CH_3	288 - 289	Calcd. for $C_9H_{13}NO_3S$. C, 50 21; H, 6.09; N, 6.51; S, 14.89 Found C, 50.05; H, 6.09, N, 6.37; S, 14 88	1629(m), 1578(w), 1175(vs), 1150(vs), 1030(vs), 783(s)	1.73(d,3H), 2.97(s,3H), 3.64(m,2H), 5.58(m,1H), 7.93 (t,2H), 8.42(t,1H), 8.95(d,1H)
Benzo[b][a]	267 - 269 (decomp.)	Calcd. for $C_{12}H_{13}NO_3S$: C, 57.35, H, 5.21; N, 5.57, S, 12.76 Found C, 57.18; H, 5.42, N, 5.50, S, 12.92	3030(w), 1622(w), 1588(w), 1230(m), 1200(m), 1043(m), 763(m)	2.04(d,3H), 3.87(m,2H), 6.31(m,1H), 7.89-8.54(m,4H), 8.72(d,1H), 9.14(d,1H), 9.53(s,1H)
3-$NHCOCH_3$	325 - 327	Calcd. for $C_{10}H_{14}N_2O_4S$. C, 46.50, H, 5 46; N, 10.85, S, 12.41 Found: C, 45.40, H, 5.47; N, 10.72; S, 12.03	3390(m), 3226(m), 3077(m), 1631(m), 1513(m), 1342(m), 1302 - (m), 1212(s), 1176(s), 1035(s), 1017(m), 783(m)	1.83(m,6H), 2.27(s,3H), 3.64(m,2H), 5.08(m,1H), 7.74 (m,2H), 8.27(m,2H)
3-CH_3	297 - 298 (decomp.)	Calcd. for $C_9H_{13}NO_3S$: C, 50.21; H, 6 09, N, 6.51; S, 14 89 Found: C, 50.09, H, 6.12; N, 6.45; S, 14.72	2907(m), 1511(m), 1263(m), 1214(vs), 1186(vs), 1172(s), 1152(s), 1032(vs), 773(s), 691(m)	1.84(d,3H), 2.62(s,3H), 5.27(m,1H), 8.03(m,2H), 8.45 (d,1H), 8.65(d,2H)
2-CH_2CH_3	m.p. 280 - 282	Calcd. for $C_9H_{13}NO_3S$: C, 49 98; H, 6.52; N, 6.48; S, 14.63 Found: C, 50.13; H, 6.42; N, 6.39; S, 14.71	3035(s), 1635(s), 1240(s), 1225(s), 1200(vs), 1175(vs), 1155(s), 1035(vs), 805(m), 782(s)	1.46(t,3H), 1.90(d,3H), 3.35(q,2H), 3.68(m,2H), 5.64 (m,1H), 8.00(m,2H), 8.46(t,1H), 8.96(m,1H)

(a) i.e. quinoline

at 25.0° and pH 4.0. After the reaction was judged to be complete, the pH was raised to 7.0 and the aqueous solution extracted several times with ether. The aqueous layer was then evaporated to dryness, dissolved in 1 - 2 mL of water and eluted down a column containing Rexyn 300 (HOH) deionizing resin. Evaporation of the eluant gave a colorless residue (80 mg) which was recrystallized from 95% alcohol. The m.p., mixed m.p. (255 - 257°) and the ^{1}H n.m.r. spectrum (D_2O) of this material were identical with those of an authentic specimen of the pyridine betaine (25a).

General Procedure for Determining the Products and Relative Proportions of Products for Reactions of (8) and (12) with Substituted Pyridines in Water Containing 0.1 M Potassium Chloride at 25.0°

The reaction products (and their relative proportions) for the reactions of 8 and 12 with substituted pyridines were determined using initial concentrations of sulfonyl chloride in the range $1.0 - 16 \times 10^{-3}$ M. A sufficient amount of the substituted pyridine base was employed in these reactions to ensure pseudo first order conditions, and to exceed the uncatalysed hydrolysis reaction of 8 or 12 by a factor of at least 50. This was done so that the relative proportions of the products would not be subject to large corrections for the presence of any alkenesulfonate anion derived from the uncatalysed hydrolysis reaction. After completion of the reaction, the pH was usually raised to at least one pH unit above the apparent pK_a of the substituted pyridine, and the solution extracted with ether. Evaporation of the aqueous layer gave a residue whose ^{1}H n.m.r. spectrum (D_2O) was compared with authentic spectra of the pyridine betaines (25), (26) and alkenesulfonate anions (19), (21). Integration of the methylene protons of the betaine and

the vinyl protons of the alkenesulfonate anion gave the relative proportions of the products (expressed as % betaine, defined in Table 1.8). These data were then converted to q values (q = % betaine/(%betaine + % alkenesulfonate anion))and then corrected for the generation of any alkenesulfonate anion derived from any uncatalysed hydrolysis reaction (corrected q is defined in Table 1.14). The reaction conditions and the % betaine for each reaction are given in Tables 1.8, 1.30, 1.31. The corrected q values for these experiments are given in Tables 1.14, 1.15.

Preparation of N-[2-Chlorosulfonylethyl]pyridinium Chloride (28a)

Freshly prepared pyridine hydrochloride (1.6 g, 1.4×10^{-2} mol) was dissolved in dry methylene chloride (20 mL). To this solution ethenesulfonyl chloride (8) (1.7 g, 1.34×10^{-2} mol) was added dropwise over one minute. The immediately formed colorless precipitate was filtered in the cold and washed with pentane, yield 2.4 g (72%); m.p. 103 - 105°C; ^{1}H n.m.r. (CD_3NO_2) δ: 5.02 (t, 2H), 5.57 (t, 2H), 8.26 (m, 2H), 8.76 (t, 1H), 9.40 (d, 2H); i.r. (nujol) 1640 (m), 1495 (m), 1376 (s), 1168 (s), 835 (w), 755 (m), 667 (s) cm^{-1}. Anal. calcd. for $C_7H_9Cl_2NO_2S$: C, 34.72; H, 3.75; Cl, 29.28; N, 5.79; S, 13.22. Found: C, 34.97; H, 4.03; Cl, 29.32; N, 5.71; S, 13.09.

Solvolysis of N-[2-Chlorosulfonylethyl]pyridinium Chloride (28a) in Water at 25.0°

The sulfonyl chloride (28a) (0.090 g, 3.7×10^{-4} mol) was added to a solution of water (50 mL) containing potassium chloride (0.400 g,

TABLE 1.30

Relative Proportions of Products from Reactions of Ethenesulfonyl Chloride (8) with Pyridines in 0.1 M Potassium Chloride at 25.0°

Pyridine	pH	$10^3 \cdot$[Pyridine] (M)[a]	$10^2 \cdot$[S] (M)[b]	% Betaine (25)
3,4-$(CH_3)_2$	4.0	0.5	1.6	87
3,5-$(CH_3)_2$	4.0	1.2	1.6	83
4-CH_3	4.0	2.0	1.6	87
4-CH_2CH_3	4.0	2.5	1.0	83
3-CH_3	4.0	4.2	1.6	86
H	3.0	1.0	1.6	80
3-$NHCOCH_3$	3.0	2.8	1.2	65
4-CO_2CH_3	3.0	30	1.2	52
3-$CONH_2$	4.0	66	0.1	~50
3-CN	3.0	120	1.2	17
2-CH_3	4.0	2.5	0.5	55
2-CH_2CH_3	5.0	10	0.5	85
2,6-$(CH_3)_2$	7.0	200	1.6	66
Benzo[b]-	4.0	30	0.8	51
2,4,6-$(CH_3)_3$	7.0	400	0.8	65

a) concentration of free substituted pyridine base.

b) initial concentration of sulfonyl chloride.

TABLE 4.31

Relative Proportions of Products from Reactions of Pyridines with trans-1-Propene-1-sulfonyl Chloride (12) in 0.1 M Potassium Chloride at 25.0°

Pyridine	pH	$10^2 \cdot$[Pyridine] (M)	$10^2 \cdot$[S] (M)	% Betaine (26)
3,4-$(CH_3)_2$	5.0	0.8	1.5	74
3,5-$(CH_3)_2$	5.0	1.6	1.5	69
4-CH_3	5.0	3.0	1.6	73
3-CH_3	4.0	0.65	1.5	65
H	4.0	1.6	0.9	56
3-$NHCOCH_3$	4.0	2	0.8	43
4-CO_2CH_3	4.0	6	0.9	26
3-CN	4.0	15	0.12	8
2-CH_3	6.0	20	~1	39
2-CH_2CH_3	7.0	2.0	0.1	64
Benzo[b]-	6.0	6	0.5	35

5.36×10^{-3} mol) at pH 4.0 and 25.0°. The pH-stat apparatus was employed with 1.0 M sodium hydroxide solution. After one hour the solvent was evaporated and the residue investigated by ^{1}H n.m.r. spectroscopy. The spectrum (D_2O) indicated the presence of the betaine (25a) and ethenesulfonate anion (19) in relative proportions 88% and 12% respectively.

Reaction of N-[2-Chlorosulfonylethyl] pyridinium Chloride (28a) with Pyridine in Water 25.0°

The sulfonyl chloride (28a) (0.150 g, 5.6×10^{-3} mol) was added to a solution of pyridine (2.0 mL, 2.48×10^{-2} mol) and potassium chloride (0.400 g, 5.36×10^{-3} mol) in water (50 mL) at pH 4.0 and 25.0°. The pH-stat apparatus was employed with 1.0 M sodium hydroxide solution. After 30 minutes the pH was adjusted to 7.5 and the solution extracted several times with ether. The aqueous layer was evaporated to dryness.

The ^{1}H n.m.r. spectrum (D_2O) of the colorless residue indicated the presence of the pyridine betaine (25a) and ethenesulfonate anion (19), in relative proportions 83% and 17% respectively.

Solvolysis of N-[2-Chlorosulfonylethyl] pyridinium Chloride (28a) in Deuterium Oxide at 25.0°

The sulfonyl chloride (28a)(0.038 g, 1.6×10^{-4} mol) was added to a stirred solution of potassium chloride (0.400 g, 5.36×10^{-3} mol) in D_2O (50 mL) at 25.0° and pH 4.0. The pH-stat apparatus was employed with 0.54 M sodium deuteroxide titrant (prepared from sodium metal (0.125 g) and D_2O (10 mL)). After 1 hour the solvent was evaporated, and the residue examined by ^{1}H n.m.r. spectroscopy (D_2O). The pyridine

betaine (25a) and ethenesulfonate anion (19) were the observed products, with 25a comprising 86% of the relative proportion of the products. The betaine (25a) was estimated (by ^{1}H n.m.r. integration of the methylene peaks) to be ~80% monodeuterated at the methylene alpha to the sulfonate group. No deuterium was observed in the ethenesulfonate anion (19) product.

Reaction of N-[2-chlorosulfonylethyl] pyridinium Chloride (28a) with Pyridine in Deuterium Oxide at 25.0°

Freshly prepared sulfonyl chloride (28a) (0.107 g, 4.42×10^{-4} mol) was added with stirring to a solution of pyridine (1.0 mL, 1.24×10^{-2} mol) and potassium chloride (0.400 g, 5.36×10^{-3} mol) in D_2O (50 mL), maintained at pH 4.0 and 25.0° with 1.5 M sodium deuteroxide solution and the pH-stat apparatus. The reaction appeared complete after a few minutes but was allowed to continue for 15 minutes. The pH was adjusted to 6.0 and the solution was extracted several times with ether. The aqueous layer was evaporated to dryness, and the residue examined by ^{1}H n.m.r. (D_2O). Pyridine betaine (25a) and ethenesulfonate anion (19) were the observed products, with the betaine (25a) comprising 76% of the products. The betaine (25a) was estimated (by integration of the methylene absorptions at δ3.62, 5.05 ppm) to be ≥95% monodeuterated at the carbon alpha to the sulfonate group. Undeuterated ethenesulfonate anion (19) comprised the remainder of the products.

Reaction of Ethenesulfonyl Chloride (8) with Pyridine in Deuterium Oxide at 25.0°C

A solution of ethenesulfonyl chloride (8) (0.029 g, 2.3×10^{-4} mol) in dry DME (0.5 mL) was injected into a stirred solution of pyridine (2.0 mL, 2.48×10^{-2} mol) and potassium chloride (0.400 g) in D_2O (50 mL) maintained at 25.0° and apparent pH 3.4 with 1.2 M sodium deuteroxide titrant solution. After 15 minutes the pH was adjusted to 7.0, and the solution extracted with ether (4 × 50 mL). The aqueous layer was then evaporated under reduced pressure to give a colorless solid. The ^1H n.m.r. spectrum (D_2O) of this material indicated the presence of pyridine betaine (25a) and ethenesulfonate anion (19) only, in relative proportions of approximately 70% and 30% respectively. There was no observable deuterium incorporation in 19, but the betaine (25a) was estimated (by integration of the absorptions at δ: 3.5, 5.0 ppm) to be ≥90% monodeuterated at the alpha carbon.

Preparation of N-[2-Chlorosulfonylethyl]pyridinium-d_5 Chloride (28b)

Freshly prepared pyridine-d_5 hydrochloride (0.550 g, 4.58×10^{-3} mol) was dissolved in methylene chloride (15 mL). To this solution, ethenesulfonyl chloride (8) (0.575 g, 4.54×10^{-3} mol) was added dropwise over 1 - 2 minutes. The immediately formed precipitate was filtered in the cold and washed with pentane, yield (0.47 g, 42%); ^{1}H n.m.r. (T-60, CD_3NO_2) δ: 5.0 (m, 2H), 5.3 (m, 2H). This compound was used without further purification.

Reaction of N-[2-Chlorosulfonylethyl]pyridinium-d_5 Chloride (28b) with Pyridine in Water at 25.0°

The sulfonyl chloride (28b) (0.160 g, 6.48×10^{-4} mol) was added to a stirred solution of pyridine (2.0 mL, 2.49×10^{-2} mol) and potassium chloride (0.400 g, 5.36×10^{-3} mol) in water (50 mL) at pH 4.0 and 25.0°. The pH-stat apparatus was employed with 1.0 M sodium hydroxide titrant solution. After 2 hours the pH was adjusted to 7.5 and the solution extracted with ether. Evaporation of the aqueous layer gave a colorless solid whose ^{1}H n.m.r. spectrum (D_2O) revealed the presence of the pyridine-d_5 betaine (25b) and ethenesulfonate anion (19), with the betaine comprising 81% of the relative proportion of the products. There was no sign of any protiated pyridine betaine (25a) in the ^{1}H n.m.r. spectrum.

Preparation of N-[2-Chlorosulfonylethyl]-2-d pyridinium Chloride (29)

Pyridine deuterochloride (0.400 g, 3.43×10^{-3} mol), prepared by bubbling DCl gas (generated by addition of oxalyl chloride (Aldrich) to D_2O) into a solution of pyridine in benzene, was dissolved in dry methylene chloride (10 mL). To this solution ethenesulfonyl chloride (8) (0.5 mL, 5.4×10^{-3} mol) was added dropwise over one minute. The immediately formed, colorless precipitate (0.50 g, 60%) was filtered in the cold and washed with methylene chloride. The sulfonyl chloride (29) was estimated to be ≥64% monodeuterated on the methylene alpha to the sulfonate group from the ^1H n.m.r. spectrum (DMSO-d_6, Merck, Sharp, Dohme) of the betaine (25) derived from reaction of 29 with this solvent. The sulfonyl chloride (29) was used without further purification.

Reaction of N-[2-Chlorosulfonylethyl]-2-d pyridinium Chloride (29) with Pyridine in Deuterium Oxide at 25.0°

The sulfonyl chloride (29) (0.150 g, 6.17×10^{-4} mol) was added to a stirred solution of pyridine (1.0 mL, 1.25×10^{-2} mol) and potassium chloride (0.400 g, 5.36×10^{-3} mol) in D_2O (50 mL) at pH 3.4 and 25.0°. The pH-stat apparatus was employed with 2.6 M sodium deuteroxide titrant solution. After 1 hour the pH was adjusted to 7.0 and the solution worked up as before. The ^1H n.m.r. spectrum (D_2O) of the residue indicated the presence of the betaine (25a) and ethenesulfonate anion (19) with 25a comprising 75% of the mixture. The relative areas of C-2:C-1 protons were 2.0:0.5 in the betaine (25a) and 2:0.6 in the ethenesulfonate (19), corresponding to 40% α monodeuterated 19.

Preparation of N-4'-methyl-[2-Chlorosulfonylethyl]pyridinium Chloride (28c)

Freshly prepared 4-picoline hydrochloride (1.0 g, 7.7×10^{-3} mol) was dissolved in dry methylene chloride (20 mL) at room temperature in an anhydrous atmosphere. Then ethenesulfonyl chloride (8) (1.0 g, 7.9×10^{-3} mol) was added dropwide over one minute. After 4 hours the solvent was evaporated to give a colorless, hygroscopic solid (1.5 g, 76%) which was washed with pentane, m.p. 80 - 85° (sealed tube); ^{1}H n.m.r. (T-60, CD_3NO_2) δ: 2.7 (s, 3H), 5.0 (t, 2H), 5.5 (t, 2H), 8.0 (d, 2H), 9.1 (d, 2H); i.r. (CH_2Cl_2) 3025 (w), 2940 (w), 2860 (w), 1640 (m), 1560 (w), 1475 (w), 1380 (s), 1168 (s), 1035 (w), 820 (w) cm^{-1}. This sulfonyl chloride (28c) was used without further purification in the following reactions.

Solvolysis of N-4'-methyl-[2-Chlorosulfonylethyl]pyridinium Chloride (28c) in Deuterium Oxide

The sulfonyl chloride (28c) (0.050 g, 2.0×10^{-4} mol) was dissolved in D_2O (∿0.5 mL) and placed in an n.m.r. tube. After 1 hour at room temperature the ^{1}H n.m.r. spectrum of this material indicated the presence of 4-picoline betaine (25c) and ethenesulfonate anion (19). The betaine (25c) was estimated to comprise ≥95% of the mixture. No deuterium was observed in either 19 or 25c.

Reaction of 4'-Methyl-[2-Chlorosulfonylethyl]pyridinium Chloride (28c) with 4-Picoline in Water at 25.0°

The sulfonyl chloride (28c) (0.100 g, 3.9×10^{-4} mol) was added to a solution of 4-picoline (3.0 mL, 3.1×10^{-2} mol) and potassium chloride (0.400 g, 5.36×10^{-3} mol) in water (50 mL) at pH 4.0 and

25.0°. The pH-stat apparatus was employed with 1.0 M sodium hydroxide titrant solution. After 15 minutes the pH was adjusted to 7.2 and the solution worked up as before. The ^{1}H n.m.r. spectrum (D_2O) of the residue indicated a 92:8 mixture of the 4-picoline betaine (25c) and ethenesulfonate anion (19).

Control Experiments

(1) Sodium Ethenesulfonate (19) with Sodium Hydroxide Solution

Sodium Ethenesulfonate (0.075 g, 5.77×10^{-4} mol) was dissolved in water (50 mL) and the pH of this solution was adjusted to 12.0 with 1.0 M sodium hydroxide solution. After refluxing for 45 minutes, the pH was adjusted to 7 with concentrated HCl solution. Evaporation of the solvent gave a colorless residue whose ^{1}H n.m.r. spectrum (D_2O) indicated that only sodium ethenesulfonate was present.

(2) Sodium Ethenesulfonate (19) in Deuterium Oxide Containing Potassium Chloride at 25.0°

(a) Apparent pH 3.4

Sodium ethenesulfonate (19) (0.190 g, 1.46×10^{-3} mol) was dissolved in D_2O (50 mL) containing potassium chloride (0.400 g, 5.36×10^{-3} mol) at pH 3.4 and 25.0°. After standing for 100 minutes the solvent was evaporated. The ^{1}H n.m.r. spectrum (D_2O) of the residue showed ethenesulfonate as the only product, and it had not incorporated any deuterium.

(b) Apparent pH 10.5

Sodium ethenesulfonate (19) (0.160 g, 1.23×10^{-3} mol) was dissolved in D_2O (50 mL) containing potassium chloride (0.400 g, 5.36×10^{-3}

mol) at pH 10.5 and 25.0°. After standing for 30 minutes the pH was adjusted to 3.0 with 20% DCl/D_2O solution. Evaporation of the solvent gave a colorless solid whose ^1H n.m.r. spectrum (D_2O) indicated only ethenesulfonate anion (19), with no observable incorporation of deuterium.

(3) Sodium 2-Hydroxyethanesulfonate (20) with Sodium Deuteroxide Solution

Sodium 2-Hydroxyethanesulfonate (0.146 g, 1.00×10^{-3} mol) was dissolved in D_2O (2 mL). In a separate flask 0.08 M sodium deuteroxide solution was prepared from sodium metal (0.045 g, 2.0×10^{-3} mol) and D_2O (25 mL). The two solutions were combined and the resulting solution allowed to stand at room temperature for 2 hours. The apparent pH of the solution was adjusted to 7 with 20% DCl/D_2O solution, and the solvent evaporated to give a colorless solid. The ^1H n.m.r. spectrum (D_2O) of this material showed only natural abundance sodium 2-hydroxyethanesulfonate (20) present.

(4) Pyridine Betaine (25a) and Sodium Ethenesulfonate (19) with Pyridine in Water Containing Potassium Chloride

Authentic specimens of pyridine betaine (25a) (0.071 g, 3.80×10^{-4} mol) and sodium ethenesulfonate (19) (0.050 g, 3.9×10^{-4} mol) were dissolved in water (50 mL) containing potassium chloride (0.400 g, 5.36×10^{-3} mol) and pyridine (1.0 mL, 1.24×10^{-2} mol) at pH 4.0. After standing at room temperature for 2 hours, the pH was adjusted to 7.0 and the solution worked up as before. The ^1H n.m.r. spectrum (D_2O) of the residue showed the betaine (25a) and ethenesulfonate anion (19) in the same relative proportion (within experimental error) as the

initial ratio.

(5) Reaction of Ethenesulfonyl Chloride (8) with Pyridine in Water Containing Potassium Chloride and Sodium Ethenesulfonate at 25.0°

Ethenesulfonyl chloride (0.100 g, 7.90×10^{-4} mol) was allowed to react with pyridine (1.0 mL, 1.24×10^{-2} mol) in water (50 mL) containing sodium ethenesulfonate (19) (0.043 g, 3.30×10^{-4} mol) and potassium chloride (0.400 g, 5.36×10^{-3} mol) at pH 4.0 and 25.0°. After 10 minutes the pH was adjusted to 7.0 and the solution worked up as previously described. The ^{1}H n.m.r. spectrum (D_2O) of the crude products indicated the presence of pyridine betaine (25) and ethenesulfonate anion (19), with the betaine (25a) comprising 60% of the relative proportion. This relative proportion was in agreement with the theoretical value of q for the reaction of 8 with pyridine and the amount of 19 initially present in solution.

Determination of Equilibrium Constants for Substituted Pyridines

The apparent pK_a's for the substituted pyridine bases were determined by constructing titration curves (obtained by titrating a solution of the free pyridine base in 0.1 M potassium chloride with 1.00 M HCl solution), and calculating the half neutralization point of the base from the titration curve. A typical titration curve is that for pyridine at 25.0°, shown in Figure 1.12. The data for this curve is given in Table 1.32. For those pyridine bases whose observed pK_a was found to be <4.0, a correction factor (to account for any hydrolysis reaction by the conjugate acid of the base) was estimated (see Appendix 2), and

TABLE 1.32

Measurement of the pK_a of Pyridine at 25.0° in 0.1 M Potassium Chloride

pyridine concentration: 2.5×10^{-2} M

titrant: 1.00 M HCl

Titre (mL)	pH
0.000	8.10
0.0100	8.02
0.0320	7.65
0.0510	7.15
0.0700	6.88
0.0900	6.70
0.1100	6.57
0.1510	6.37
0.2000	6.20
0.2520	6.04
0.3000	5.92
0.3500	5.82
0.4000	5.73
0.4600	5.61
0.5100	5.54
0.5810	5.42
0.6400	5.33
0.7000	5.24
0.8000	5.07
0.8500	4.98
0.9510	4.80
1.0200	4.64
1.1010	4.40
1.1310	4.28
1.1500	4.19
1.1700	4.07
1.1900	3.94
1.2100	3.78
1.2300	3.55
1.2500	3.30
1.2700	3.05
1.3000	2.79
1.3200	2.66
1.350	2.52
1.420	2.30
1.50	2.15

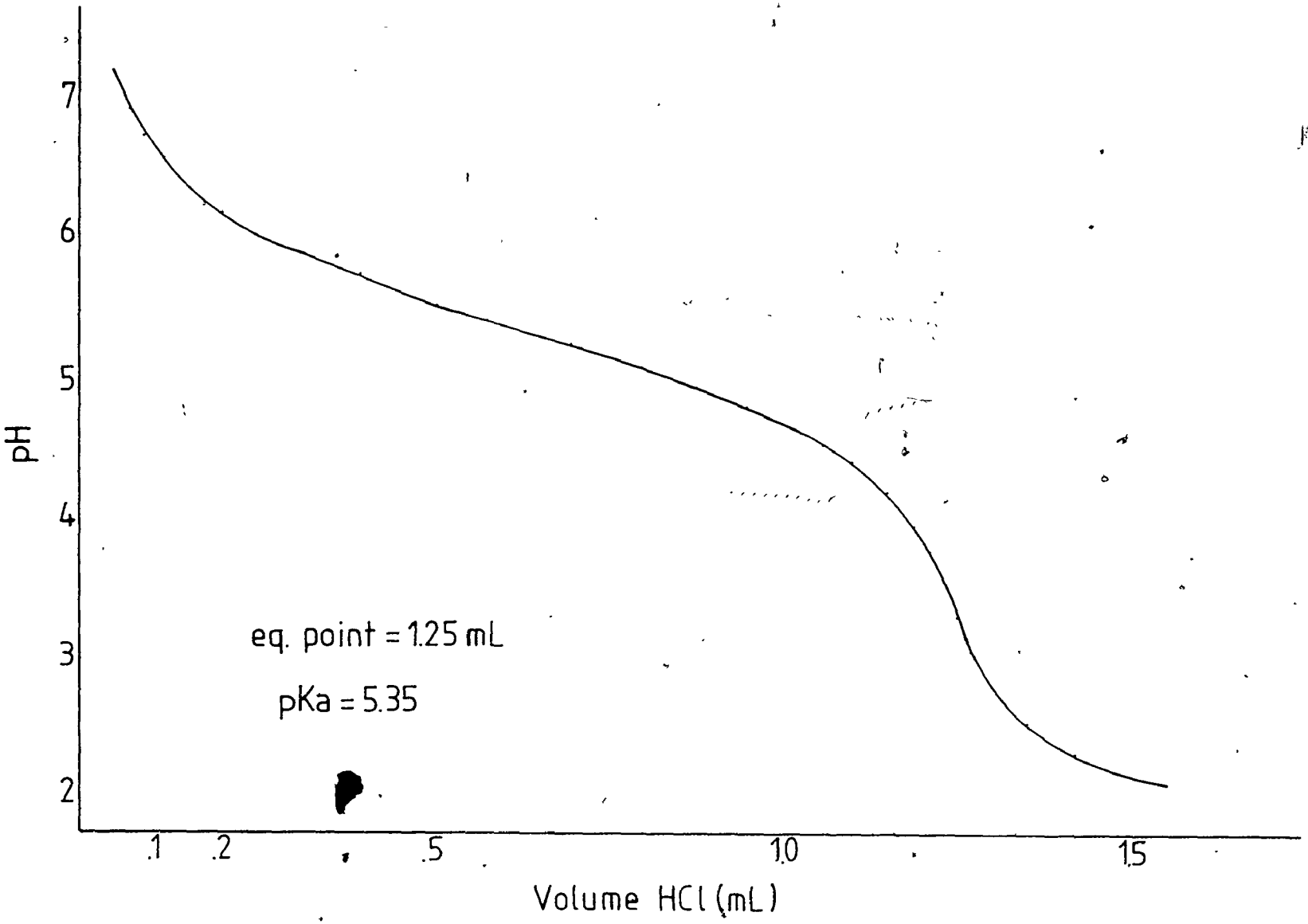


FIGURE 1.12 Titration Curve for Pyridine in Water at 25.0°C

then applied to the observed pK_a of the base. For 3-cyanopyridine the literature (77) value of the pK_a in water at 25.0° was used. The corrected pK_a values are given in Tables 1.10, 1.17, 1.24, 1.25.

Procedure for Kinetic Determinations

The kinetics of the solvolysis reactions of the sulfonyl chlorides were determined using the pH-stat technique (51,76). The reactions were initiated by injection (using a 100 µL syringe) of an aliquot (usually 100 µL) of a solution of the sulfonyl chloride in DME (~1 mL) into the reaction solution previously set at the desired pH and temperature. All reaction solutions (50 mL) were prepared volumetrically using distilled water, potasisum chloride (0.40 g, 5.4×10^{-3} mol, 0.11 M) and the appropriate amount of the substituted pyridine base. The aqueous DME reaction solution mixtures were prepared by adding DME (15 mL and 25 mL for 30% and 50%, respectively) to the flask containing potassium chloride and the pyridine base, and then filling to the mark with distilled water. The initial sulfonyl chloride concentrations used were in the range 4×10^{-4} - 3×10^{-3} M. The rate of the solvolysis reaction was then monitored by recording the volume of titrant (prepared from sodium hydroxide concentrate using distilled water) delivered with time.

In this study care was taken to avoid very low pH's and buffered solutions, conditions in which the pH-stat technique is inappropriate owing to the poor response of the glass electrode as the reaction proceeds. It was found that reactions with half lives from 0.25 min. to several hours could be measured, but most of the reactions studied

here were in the range 0.5 - 10 min. The accuracy of the method was tested by determining the rate constant for p-toluenesulfonyl chloride: k_ψ was observed to be 3.54×10^{-3} s^{-1} at pH 4.0 and 25.0°. This value of k_ψ compared favorably with literature values (10) in the range 3.00 - 3.85×10^{-3} s^{-1}.

Pseudo first order plots of $\log(V_\infty - V_t)$ versus time were constructed from the volume of sodium hydroxide titrant delivered with time, and best straight lines were fitted by inspection. Three typical first order plots are shown in Figures 1.13 - 1.15, with the data for these plots given in Tables 1.33 - 1.35. The pseudo first order rate constants (k_ψ) were then calculated from the slopes of these lines. These rate constants are given in Tables 1.2, 1.3, 1.6, 1.9 - 1.11, 1.17, 1.22 - 1.25.

Second order rate constants (k_B's) were determined by the least squares analysis of plots of k_ψ versus free pyridine base concentration. The free pyridine base concentrations were determined from the observed pK_a, the pH of the kinetic run and the Henderson-Hasselbalch equation (76):

$$pH = pK_a + \log\left(\frac{BH^+}{B}\right)$$

$[B]$ = free pyridine concentration

$[BH^+]$ = protonated pyridine concentration

The coefficients for the Brönsted equations were determined by least squares analysis of plots of $\log k_B$ versus pK_a for the unhindered pyridines.

TABLE 1.33

Uncatalysed Hydrolysis of Ethenesulfonyl Chloride (8) in Water at 25.0°C

pH: 4.0

titrant concentration: 0.100 M NaOH

potassium chloride: 0.1 M

sulfonyl chloride concentration: 6.3×10^{-4} M

Time (min.)	Titre (mL)	$V_\infty - V_t$ (mL)
2.50	0.0965	0.4359
5.00	0.1715	0.3600
9.00	0.2661	0.2654
13.00	0.3350	0.1965
17.00	0.3854	0.1461
21.50	0.4276	0.1039
25.00	0.4510	0.0805
31.00	0.4792	0.0523
37.00	0.4970	0.0345
44.00	0.5112	0.0203
59.00	0.5240	0.0075
> 100	0.5315	

$k_\psi = 1.27 \times 10^{-3}\ s^{-1}$

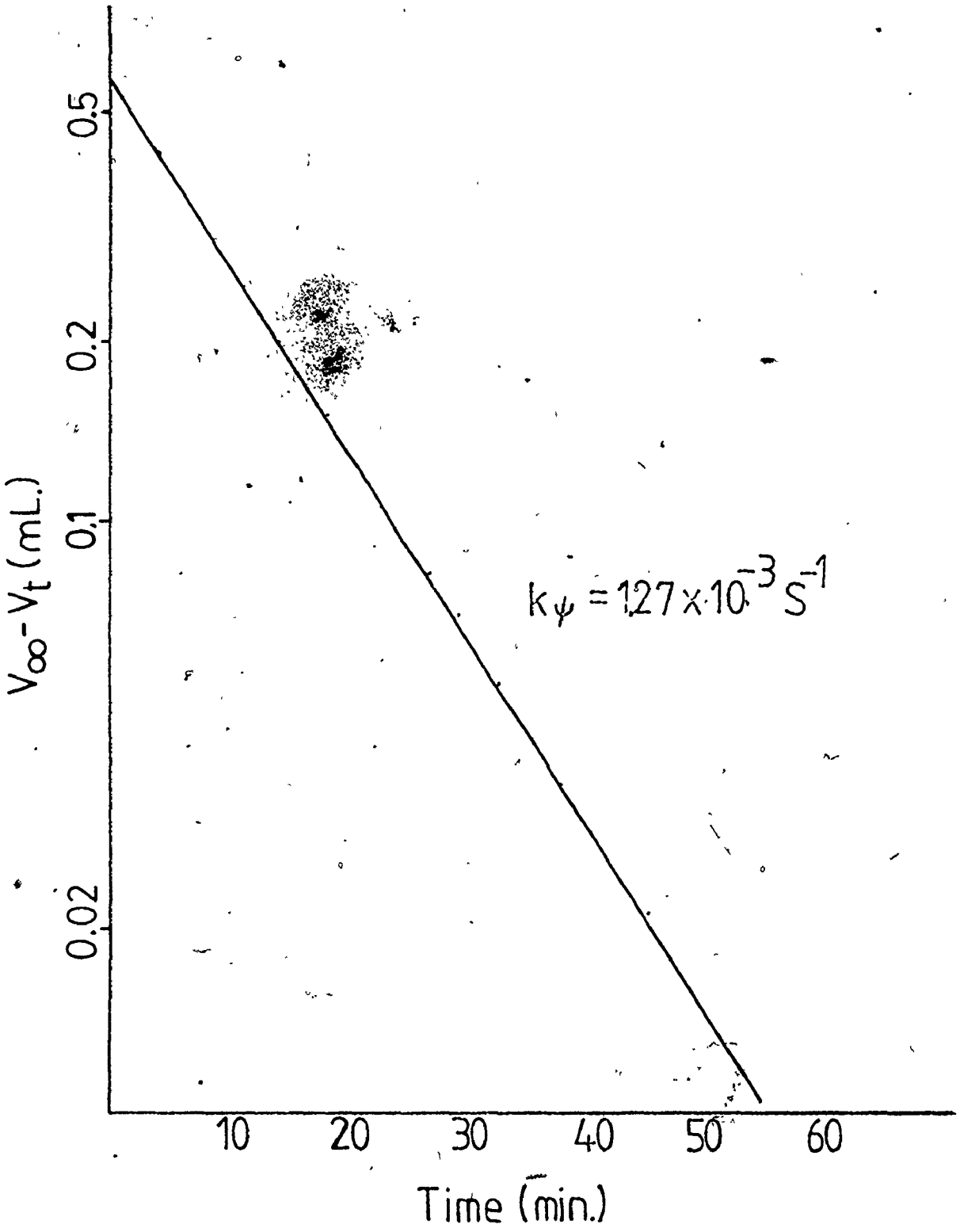


FIGURE 1.13 Uncatalysed Hydrolysis of Ethenesulfonyl Chloride (8) in Water at 25.0°C and pH 4.0

TABLE 1.34

Uncatalysed Hydrolysis of Ethenesulfonyl Chloride (8) in Water at 25.0°C

pH: 9.0

sulfonyl chloride concentration: 1.0×10^{-3} M

titrant: 1.00 M NaOH

Time (min.)	Titre (mL)	$V_\infty - V_t$ (mL)
1.20	0.0396	0.0851
2.20	0.0519	0.0728
3.00	0.0614	0.0633
4.50	0.0749	0.0498
6.00	0.0853	0.0394
8.00	0.0960	0.0287
10.50	0.1053	0.0194
13.00	0.1114	0.0133
16.00	0.1164	0.0083
19.00	0.1195	0.0052
23.00	0.1219	0.0028
> 50	0.1247	

$$k_{observed} = 2.65 \times 10^{-3}\ s^{-1}$$

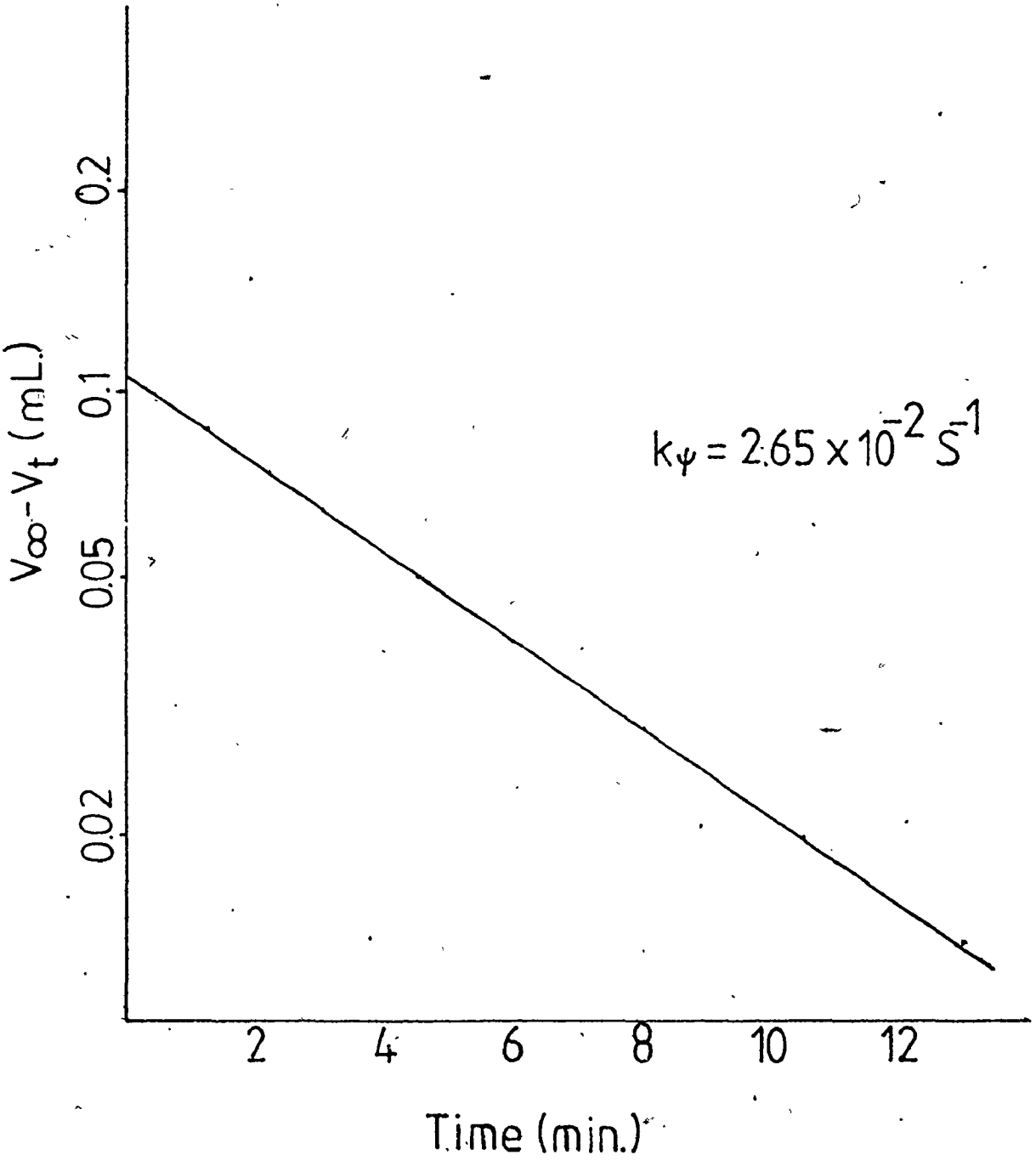


FIGURE 1.14 Uncatalysed Hydrolysis of Ethenesulfonyl Chloride (8) in Water at 25.0°C and pH 9.0

TABLE 1.35

Reaction of Ethenesulfonyl Chloride (8) with Pyridine in Water at 25.0°C

pH: 3.5

total pyridine concentration: 3.23×10^{-2} M

titrant concentration: 1.00 M NaOH

potassium chloride: 0.1 M

sulfonyl chloride concentration: 1.6×10^{-3} M

Time (min.)	Titre (mL)	$V_\infty - V_t$ (mL)
0.25	0.0258	0.1034
0.50	0.0461	0.0831
0.75	0.0620	0.0672
1.00	0.0748	0.0544
1.30	0.0873	0.0419
1.80	0.1025	0.0267
2.20	0.1093	0.0200
2.60	0.1168	0.0124
3.10	0.1231	0.0061
4.4	0.1292	

$$k_\psi = 1.44 \times 10^{-2}\ s^{-1}$$

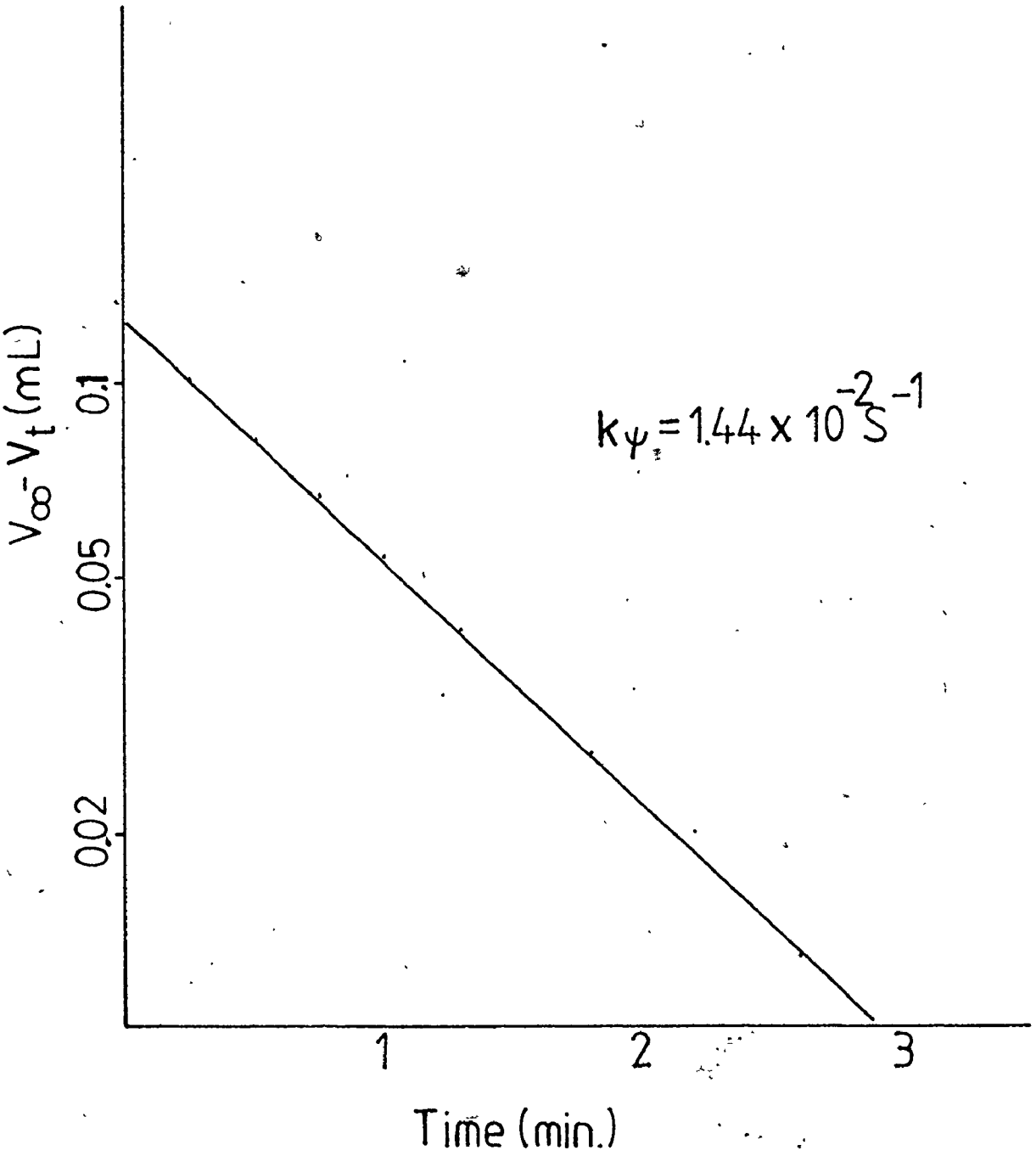


FIGURE 1.15 Reaction of Ethenesulfonyl Chloride (8) with Pyridine in Water at 25.0°C and pH 3.5

Determination of Y-values for Aqueous Mixtures of 1,2-Dimethoxyethane Containing 0.1 M Potassium Chloride at 25.0°

Y-values for 30% and 50% aqueous DME solvent mixtures containing 0.1 M potassium chloride were determined by the method of Fainberg and Winstein (60) using 2-chloro-2-methylpropane (BDH, distilled from P_2O_5 before use). In these solvolyses, the initial concentration of the substrate was $\leq 5 \times 10^{-4}$ M. The rate constants for the solvolysis of the alkyl chloride in these solvents were determined using the pH stat technique as previously described. The Y-values were calculated from the rate constants (k_ψ) using the equation: $\log(k_\psi/k_0) = mY$ where $m = 1$ and $k_0 = 9.26 \times 10^{-6}$ s^{-1} for solvolysis in 80% aqueous ethanol. The results are given in Table 1.22.

CHAPTER 2

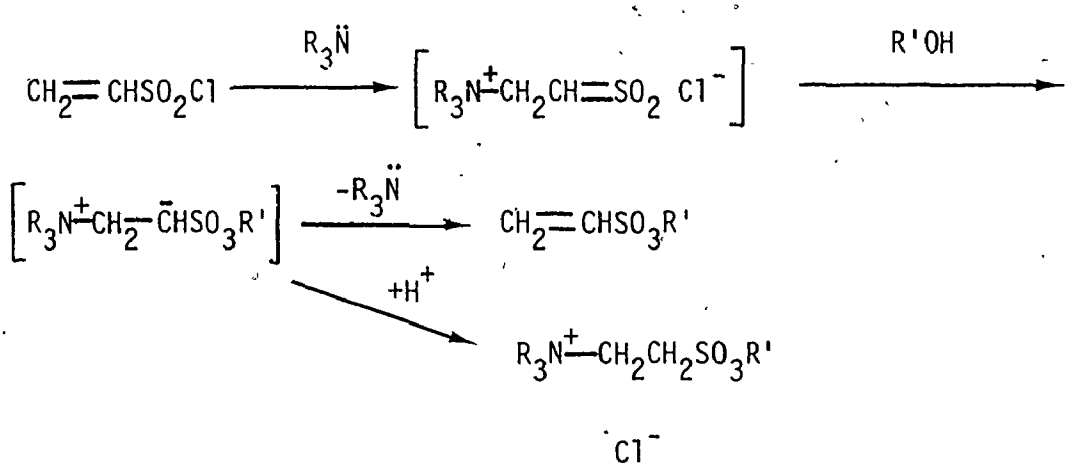
REACTIONS OF ETHENESULFONYL CHLORIDE AND N-PYRIDINIOETHANESULFONYL CHLORIDE WITH PYRIDINE IN NITROMETHANE CONTAINING NEOPENTYL ALCOHOL

2.1 Introduction

The previous chapter dealt with the reactions of two simple alkenesulfonyl chlorides with substituted pyridine bases in an aqueous medium. To the organic chemist however, this medium is usually of limited synthetic importance. Consequently, the study of the reactions of these sulfonyl chlorides in an organic medium would appear to be more practical, especially since "[2]betylates" have recently been shown to be useful intermediates for organic synthesis (1,2,3).

In a series of experiments under varying reaction conditions King and Loosmore (4,5) showed that the reaction of ethenesulfonyl chloride (1) with tertiary amines and primary and secondary alcohols or phenols in methylene chloride, always resulted in the formation of an ethenesulfonate ester and a [2]betylate. The ethenesulfonate ester made up approximately 60% of the mixture, and was concluded (4) to have been derived by a vinylogous nucleophilic catalysis mechanism (as shown in Scheme 2.1).

SCHEME 2.1



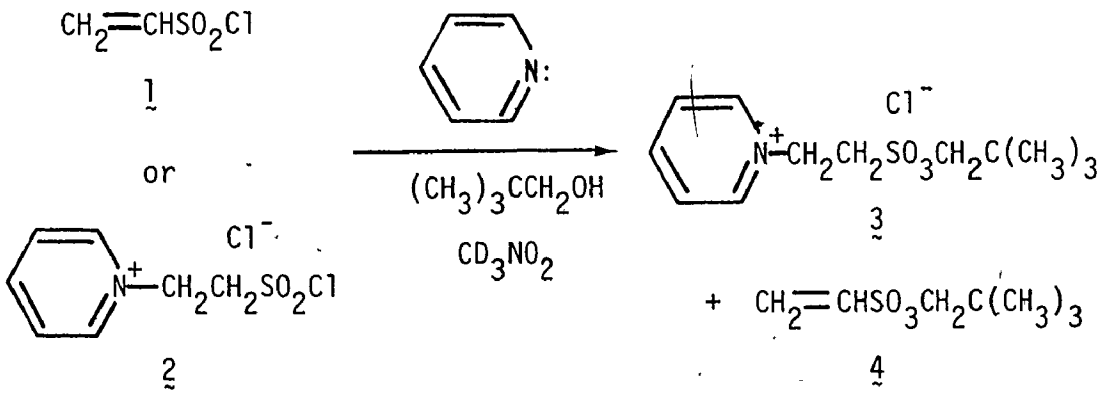
To obtain a more complete understanding of these reactions of 1, especially those using pyridine as the tertiary amine base, a brief investigation of this reaction was initiated. For this study, a few practical modifications in the reaction medium were necessary. An alcohol was required whose ethenesulfonate ester and [2]betylate would be relatively unreactive under the reaction conditions. The products should be readily identified by comparison with authentic specimens. Furthermore, all reactants and products must be soluble in the organic medium chosen for these reactions. For these reasons the reactions of ethenesulfonyl chloride (1) and N-[2-chlorosulfonylethyl]pyridinium chloride (2) with pyridine-d_5 were performed with neopentyl alcohol in nitromethane-d_3. The results of these ^{1}H n.m.r. experiments are now described.

2.2 Results and Discussion

Reactions of Ethenesulfonyl Chloride (1) and N-[2-Chlorosulfonylethyl] pyridinium Chloride (2) with Pyridine and Neopentyl Alcohol in Nitromethane at 37°C

The two sulfonyl chlorides 1, 2 were treated with pyridine-d_5 (~5 equivalents) and neopentyl alcohol (~2 equivalents) in nitromethane-d_3 in a series of ^{1}H n.m.r. experiments performed at 37° (probe temperature). In both experiments neopentyl [2]betylate chloride (3) and neopentyl ethenesulfonate (4) were the only observed products (the reactions were essentially complete one minute after injection of the pyridine and mixing the reactants), in a 1:2 relative proportion initially. (Scheme 2.2).

SCHEME 2.2



Both neopentyl ethenesulfonate (4) and neopentyl[2]betylate chloride (3) were identified by comparison with ^{1}H n.m.r. spectra (in CD_3NO_2) of authentic specimens.

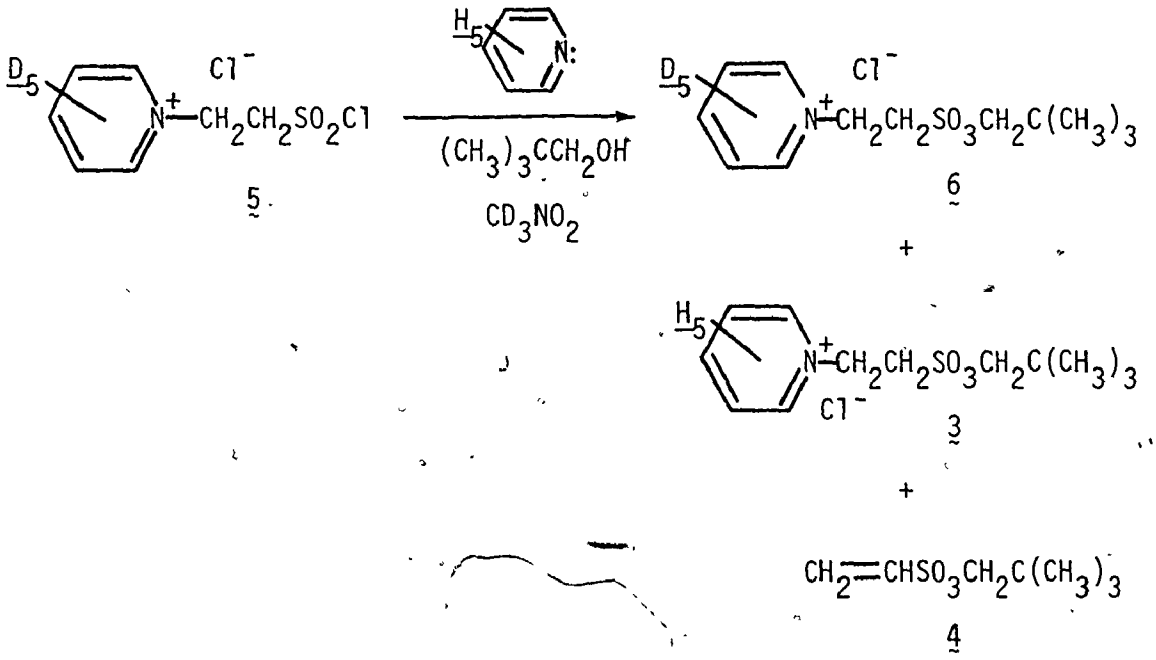
The reaction solutions were monitored by ^1H n.m.r. spectroscopy for several days. During this period the peaks ascribed to the [2]-betylate (3) (δ: 4.0, 4.3, 5.3 ppm) were observed to increase at the expense of the absorptions of neopentyl ethenesulfonate (4). After six days a relative proportion of ~88% 3 was observed (as judged by ^1H n.m.r. integration of the absorptions at δ: 3.8, 4.0 ppm). This result proved to be useful in the preparation of an authentic specimen of neopentyl [2]betylate chloride (3) from ethenesulfonyl chloride (1).

A ^1H n.m.r. experiment with neopentyl ethenesulfonate (4) in CD_3NO_2 with neopentyl alcohol and excess pyridine-d_5 showed no [2]-betylate (3) after 22 hours. The addition of 2 equivalents of pyridinium chloride to this solution resulted in the observation of 3 after only two hours at room temperature. This experiment demonstrated that pyridinium chloride was a necessary ingredient in the conversion of 4 to 3.

When N-[2-chlorosulfonylethyl]pyridinium-d_5 chloride (5) was treated with pyridine-H_5 and neopentyl alcohol in nitromethane-d_3, the [2]betylate (3) derived from this reaction was estimated (by comparison of the peaks due to the ortho aromatic protons of 3 with the singlet at δ: 4.0 ppm) to be ~80% pyridine-d_5 betylate (6), with the remainder being the completely protiated betylate (3) (Scheme 2.3).

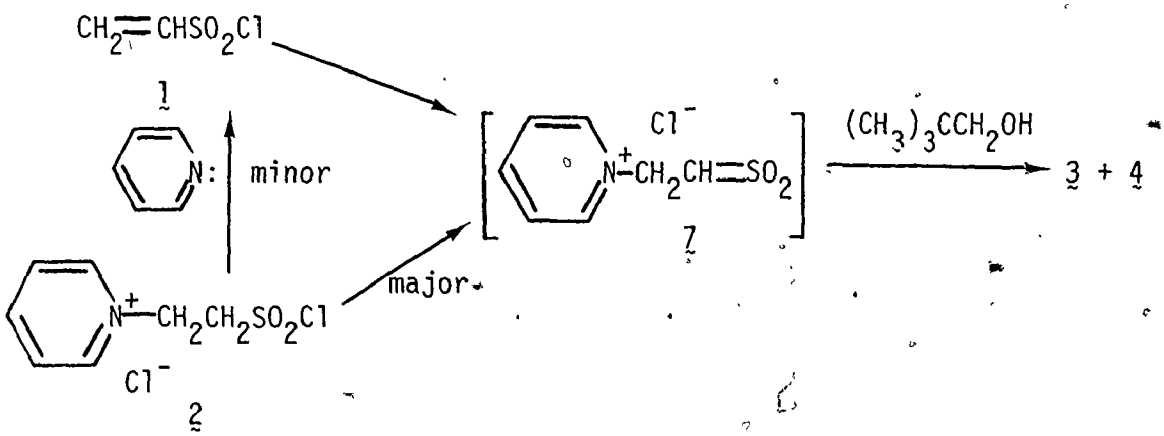
The identical product ratios obtained for the reactions of 1 and 2 with pyridine and neopentyl alcohol strongly suggests that both reactions are proceeding through a common intermediate. While this intermediate is probably the pyridiniosulfene (7), the result of the reaction with 5 and pyridine also suggests that some (~20%) of 5 (and

SCHEME 2.3



therefore 2 also) reacts by first generating ethenesulfonyl chloride (1) and then the pyridiniosulfene (7). The proposed mechanism for the formation of the observed products in these reactions is given in Scheme 2.4.

SCHEME 2.4



This scheme is only slightly more complex than that proposed by King and Loosmore (1) because it includes the mechanism of reaction of 2 as well.

For the reaction of ethenesulfonyl chloride (1) with pyridine and neopentyl alcohol, it is unlikely that 1 is converted to 2 *in situ*, since pyridinium chloride has been shown to be a necessary ingredient in the synthesis of 2 from 1 as well as 3 from 4 in organic solvents.

2.3 Conclusions

The results of the ^1H n.m.r. experiments here support the mechanism proposed by King and Loosmore (4) for the generation of [2]betylates and ethenesulfonate esters in the reactions of 1 with tertiary amines and alcohols in an organic medium.

The slow conversion of an ethenesulfonate ester to a [2]betylate in the presence of a tertiary amine and its hydrochloride salt may prove to be useful for the *in situ* preparation of some [2]betylates.

2.4 Experimental

The general comments given in Chapter 1 apply here as well. Neopentyl alcohol (Aldrich) was used as supplied. ^{1}H n.m.r. experiments were performed on a Varian T-60 ^{1}H n.m.r. spectrometer (probe temperature 37°), using tetramethylsilane (TMS) as a reference.

Neopentyl ethenesulfonate (4) was prepared by the method of Aslam (6), and used without further purification, ^{1}H n.m.r. (CD_3NO_2) δ: 0.98 (S, 9H), 3.81 (S, 2H), 6.18 - 6.81 (ABC multiplet, 3H).

Reaction of Ethenesulfonyl Chloride (1) with Pyridine-d_5 and Neopentyl Alcohol in Nitromethane-d_3

Ethenesulfonyl chloride (1) (0.017 g, 1.34×10^{-4} mol) was dissolved in nitromethane-d_3 (0.250 mL) containing neopentyl alcohol (0.020 g, 2.26×10^{-4} mol) and placed in an n.m.r. tube. To this solution at 37° (probe temperature) pyridine-d_5 (0.060 mL, 7.0×10^{-4} mol) was injected and the solution thoroughly mixed. The ^{1}H n.m.r. spectrum was obtained immediately (~1 minute after mixing), and showed absorptions at δ: 3.8, 4.0 (singlets), a triplet at 5.3 and a multiplet of the characteristic pattern observed with 4 (6) from 6.0 - 7.0 ppm. These peaks were identified as characteristic of neopentyl ethenesulfonate (4) and neopentyl [2]betylate chloride (3), by identification with ^{1}H n.m.r. spectra of authentic specimens. The relative proportions of 3 and 4 were determined by integration of the singlets at 3.8, 4.0 ppm to be 33% and 67%, respectively. After 6 days at 37° the relative proportion of 3 was determined to be 88%.

Reaction of N-[2-Chlorosulfonylethyl] pyridinium Chloride (2) with Neopentyl alcohol and Pyridine-$\underline{d}_5$ in Nitromethane-$\underline{d}_3$

The sulfonyl chloride (2) (0.025 g, 1.03×10^{-4} mol) was mixed with neopentyl alcohol (0.014 g, 1.6×10^{-4} mol) and nitromethane-$\underline{d}_3$ (250 µL) in an n.m.r. tube at 37° (probe temperature). To this mixture pyridine-$\underline{d}_5$ (45 µL, 5.3×10^{-4} mol) was injected. After thorough mixing the ^{1}H n.m.r. spectrum was obtained (∿1 minute after injection of pyridine). The spectrum showed absorptions identical to those described above, indicating the presence of neopentyl ethenesulfonate (4) and neopentyl [2]betylate chloride (3) in relative proportions 67% and 33%, respectively. After 45 hours at 37° the ^{1}H n.m.r. spectrum of the solution showed a relative proportion of 3 of 88%. No other products were observed in this reaction.

Reaction of N-[2-Chlorosulfonylethyl] pyridinium-$\underline{d}_5$ Chloride (5) with Pyridine in Nitromethane

Freshly prepared pyridinio-$\underline{d}_5$ sulfonyl chloride (5) (0.027 g, 1.09×10^{-4} mol) was mixed with neopentyl alcohol (0.017 g, 1.92×10^{-4} mol) and nitromethane-$\underline{d}_3$ (400 µL) at 37° in an n.m.r. tube. Pyridine (50 µL, 6.2×10^{-4} mol) was injected into the mixture and thoroughly shaken. The ^{1}H n.m.r. spectrum of the resulting solution was obtained immediately. The absorptions in the spectrum indicated the presence of neopentyl ethenesulfonate (4) and the pyridine-$\underline{d}_5$ [2]betylate (6), along with the absorption at δ: 9.4 which was ascribed to the completely protiated [2]betylate (3). Comparison of the multiplet at δ: 9.4 ppm with the singlet at 4.0 ppm (for 3) resulted in an estimated relative

proportion of 20% of 3 in total amount of 3 and 6 formed in the reaction.

Control Experiment

Neopentyl Ethenesulfonate (4) with Pyridine and Neopentyl Alcohol in Nitromethane-d_3

Neopentyl ethenesulfonate (4) (0.030 g, 1.69×10^{-4} mol) was dissolved in nitromethane-d_3 (0.40 mL) containing neopentyl alcohol (0.060 g, 6.8×10^{-4} mol) at room temperature. Pyridine-d_5 (0.075 mL, 9.0×10^{-4} mol) was added, and the solution monitored by ^{1}H n.m.r. spectroscopy for 24 hours. After this period of time no reaction was observed. To this solution pyridine-d_5 hydrochloride (0.040 g, 3.33×10^{-4} mol) was added, and the solution monitored for a further 22 hours. The presence of neopentyl [2]betylate chloride (3) was initially observed in the ^{1}H n.m.r. spectrum after 2 hours, eventually making up ~85% of the mixture of 3 and 4 after 22 hours at room temperature (both α monodeuterated and undeuterated 3 were observed).

Preparation of N-2-[(2',2'-Dimethylpropoxy)sulfonylethyl] pyridinium Chloride (Neopentyl [2]Betylate Chloride) (3)

Ethenesulfonyl chloride (1) (0.880 g, 7.0×10^{-3} mol) was combined with neopentyl alcohol (0.650 g, 7.4×10^{-3} mol) in methylene chloride (30 mL) at room temperature. Pyridine (2.5 mL, 3.1×10^{-2} mol) was injected and the solution allowed to stand for 8 days; the reaction mixture turned orange in color and deposited colorless needles during this time. The precipitate was filtered and was recrystallized from

dry acetonitrile (1.3 g, 65%), m.p. 154 - 155°; ^{1}H n.m.r. (CD_3CN) δ: 0.93 (s, 9H), 4.01 (s, 2H), 4.21 (t, 2H), 5.18 (t, 2H), 8.11 (t, 2H), 8.60 (t, 1H); 9.28 (d, 2H); ^{1}H n.m.r. (CD_3NO_2) δ: 0.92 (s, 9H), 4.02 (s, 2H), 4.26 (t, 2H), 5.36 (t, 2H), 8.22 (t, 2H), 8.62 (m, 1H), 9.36 (d, 2H); i.r. (nujol) 3130 (w), 3075 (m), 1635 (m), 1335 (s), 1268 (s), 1200 (vs), 1135 (s), 1050 (s), 950 (s) cm^{-1}; Anal. Calcd. for $C_{12}H_{20}ClNO_3S$: C, 49.06; H, 6.86; N, 4.77; S, 10.91; Cl, 12.07. Found: C, 49.25; H, 6.82; N, 4.83; S, 10.99; Cl, 12.01.

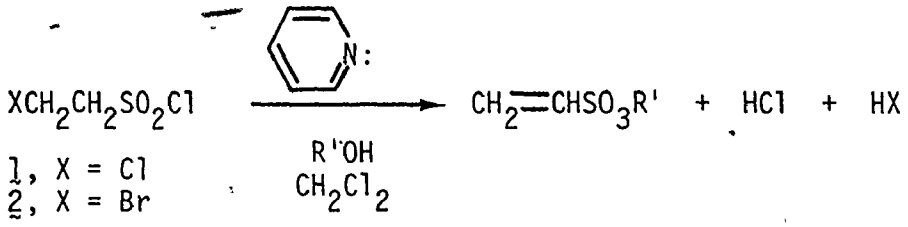
CHAPTER 3

REACTIONS OF 2-SUBSTITUTED ETHANESULFONYL CHLORIDES WITH PYRIDINE IN NITROMETHANE CONTAINING NEOPENTYL ALCOHOL

3.1 Introduction

In the 1940's Whitmore and Landau (1) showed that the reaction of 2-chloroethanesulfonyl chloride (1) or 2-bromoethanesulfonyl chloride (2) with pyridine and an alcohol in methylene chloride (CH_2Cl_2) at 0°C resulted in modest yields (25 - 60%) of the ethenesulfonate ester (as shown in Scheme 3.1). No other sulfonate esters were reported in these reactions.

SCHEME 3.1

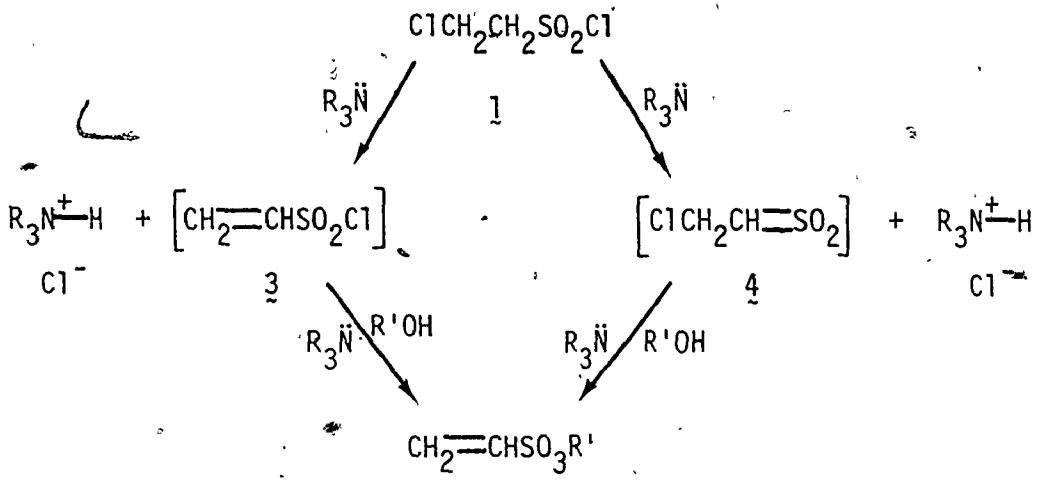


The mechanism by which the ethenesulfonate ester is formed in this reaction, as well as the general question of the manner in which beta (β) substituted ethanesulfonyl chlorides react with tertiary (3°) amines remained uninvestigated prior to the present study.

Reactions such as that shown in Scheme 3.1 may be imagined to proceed by two pathways, illustrated in Scheme 3.2 for the specific case of 2-chloroethanesulfonyl chloride (1). The elimination reaction of (1) may generate ethenesulfonyl chloride (3) or the chloromethylsulfene (4).

This potential for mechanistic duality in the elimination reactions of these beta substituted ethanesulfonyl chlorides should be present in organic and aqueous solvents. However, the relative ease of these

SCHEME 3.2

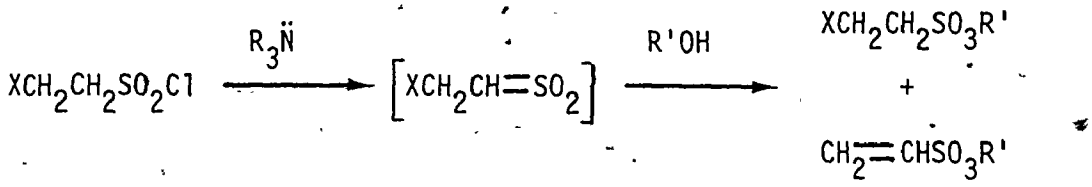


two pathways could be dependent upon the nature of the nucleofuge present at the beta carbon, as well as perhaps the solvent and possibly even the base used.

From the results of Chapter 2 the reaction of ethenesulfonyl chloride (3) with pyridine and a primary alcohol in nitromethane has been well established. Therefore the observation of a 1:2 mixture of [2]betylate and ethenesulfonate ester in the reaction of a beta substituted ethanesulfonyl chloride under these conditions would signify a common reaction pathway for 3 and the β-substituted ethanesulfonyl chloride.

If treatment of a β-substituted ethanesulfonyl chloride with a tertiary amine resulted in the formation of a reactive substituted methylsulfene intermediate, then it would be trapped by the primary alcohol present. The trapping of this sulfene intermediate with the alcohol might be expected to result in significant proportions of the beta-substituted ethanesulfonate ester (and possibly some ethenesulfonate ester), as shown in Scheme 3.3.

SCHEME 3.3



A few beta substituted ethanesulfonyl chlorides have been prepared by various routes (2, 3, and Chapter 4), and have been well characterized. Therefore, there appears to be a method to determine the mechanism of the tertiary amine promoted elimination reaction of a series of beta substituted ethanesulfonyl chlorides by the nature of the reaction products.

Several beta substituted ethanesulfonyl chlorides were prepared, and the results of their reactions with pyridine in the presence of neopentyl alcohol in nitromethane are now presented.

3.2 Results and Discussion

Reactions of Beta Substituted Ethanesulfonyl Chlorides with Pyridine and Neopentyl Alcohol in Nitromethane-d_3 at 37°C

In several ^1H n.m.r. experiments, 2-chloroethanesulfonyl chloride (1), 2-acetoxyethanesulfonyl chloride (5), 1,2-ethanedisulfonyl chloride (6) and neopentyl 2-(chlorosulfonyl) ethanesulfonate (7) were treated with pyridine-d_5 (5 equivalents) and neopentyl alcohol (~2 equivalents) in nitromethane-d_3 at 37° (probe temperature).

$ClCH_2CH_2SO_2Cl$ (1)

$CH_3COCH_2CH_2SO_2Cl$ (5)

$ClO_2SCH_2CH_2SO_2Cl$ (6)

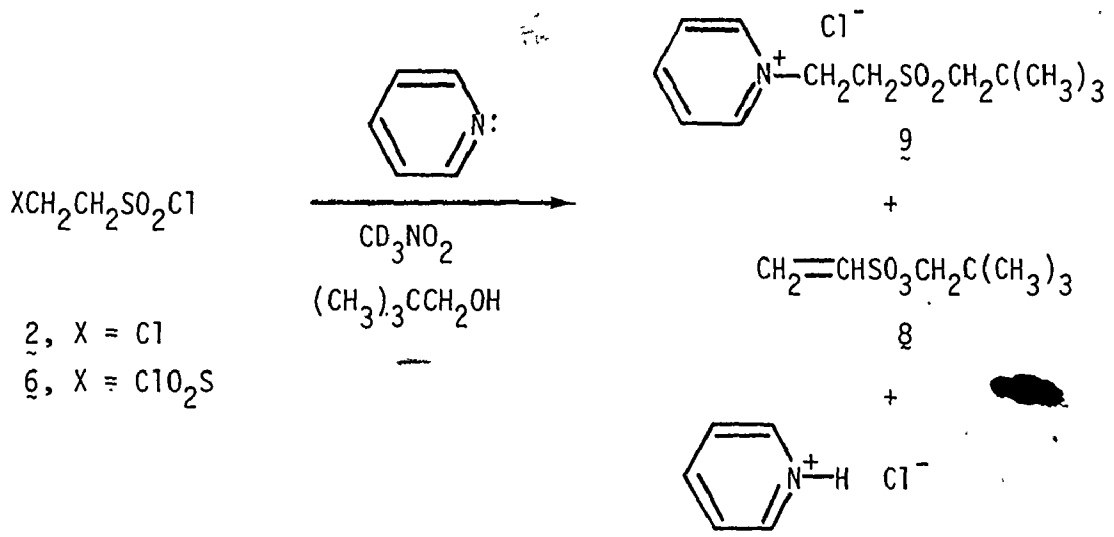
$(CH_3)_3CCH_2OSO_2CH_2CH_2SO_2Cl$ (7)

The reactions were initiated by injection of pyridine into a solution of the appropriate sulfonyl chloride in nitromethane-d_3 containing neopentyl alcohol. In all cases a very rapid reaction was observed (there was no sign of the starting sulfonyl chloride in the ^1H n.m.r. spectrum one minute after addition of pyridine and thorough mixing). The reaction products were identified by comparison with the ^1H n.m.r. spectra (in CD_3NO_2) of authentic specimens of these materials.

For the reactions of 2-chloroethanesulfonyl chloride (1) and 1,2-ethanedisulfonyl chloride (6) under these conditions, the reaction products were observed to be neopentyl ethenesulfonate (8) and neopentyl [2]betylate chloride (9), as shown in Scheme 3.4. There were no other

peaks in the ^1H n.m.r. spectrum (except for some of the excess neopentyl alcohol) of the crude reaction mixture.

SCHEME 3.4



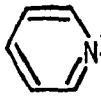
The relative proportions of 8 and 9 observed in these reactions are given in Table 3.1, along with the data for the reaction of ethenesulfonyl chloride (3) taken from Chapter 2. For the reaction of 1 in this medium it was observed that the ratio of 9:8 increased slowly with time, resulting in an ~90% relative proportion of 9 after 5 days.

In contrast to the reactions of 1 and 6, with 2-acetoxyethanesulfonyl chloride (5) the reaction products were observed to be neopentyl 2-acetoxyethanesulfonate (11) and neopentyl ethenesulfonate (8) in relative proportions 40% and 60%, respectively. This reaction is shown in Scheme 3.5.

Control experiments with authentic specimens of neopentyl 2-chloroethanesulfonate (10) and neopentyl 2-acetoxyethanesulfonate (11) showed these compounds to be stable under the reaction conditions.

TABLE 3.1

Reactions of 2-Chloroethanesulfonyl Chloride (1) and 1,2-Ethanedisulfonyl Chloride (6) with Pyridine and Neopentyl Alcohol in Nitromethane at 37°C

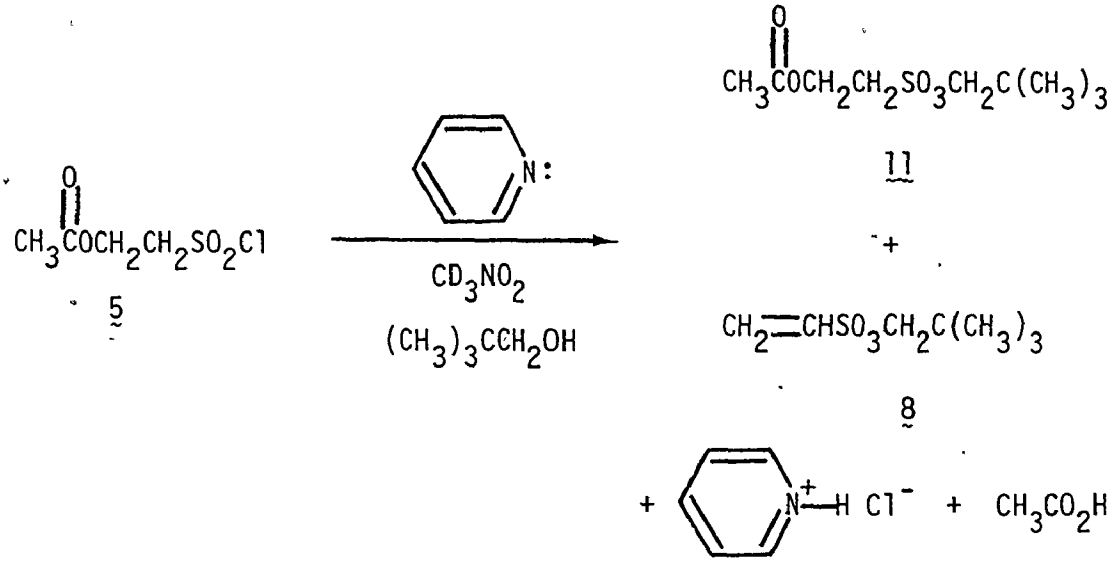
Sulfonyl Chloride	Relative Proportions of Products (%)[a]	
	$CH_2{=}CHSO_3CH_2C(CH_3)_3$ (8)	[2]betylate (9)
$ClCH_2CH_2SO_2Cl$ (1)	71(b)	29
$ClO_2SCH_2CH_2SO_2Cl$ (6)	69(c)	31
$CH_2{=}CHSO_2Cl$ (3)	67	33
 (14)	67	33

a) estimated by integration of the methylene absorptions of 8 and 9 at δ: 3.81 and 4.02 ppm about 2 minutes after injection of pyridine.

b) no sign of any $ClCH_2CH_2SO_3CH_2C(CH_3)_3$ (10) in ^1H n.m.r. spectrum.

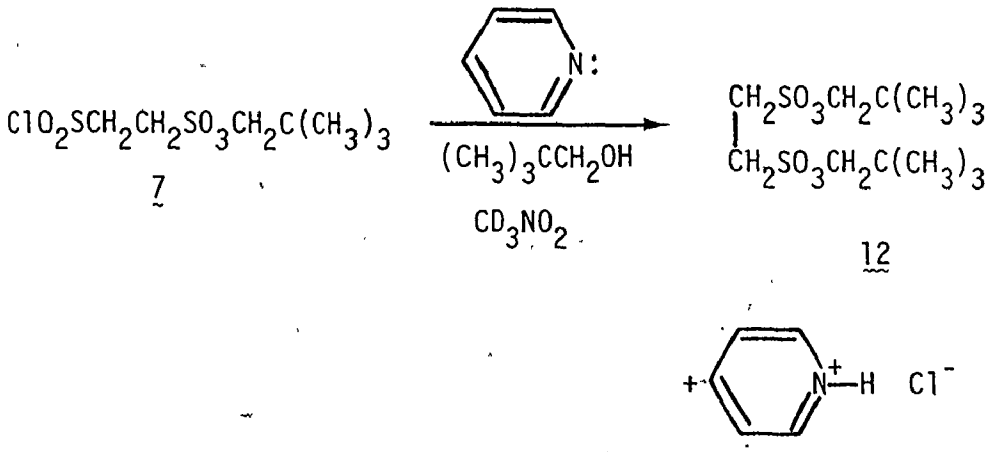
c) no sign of any $ClO_2SCH_2CH_2SO_3CH_2C(CH_3)_3$ (7) or $(CH_3)_3CCH_2O_3SCH_2CH_2SO_3CH_2C(CH_3)_3$ (12) in ^1H n.m.r. spectrum.

SCHEME 3.5



The reaction of neopentyl 2-(chlorosulfonyl)ethanesulfonate (7) with pyridine-d_5 and neopentyl alcohol resulted in the formation of dineopentyl-1,2-ethanedisulfonate (12), as shown in Scheme 3.6. No other reaction products were observed.

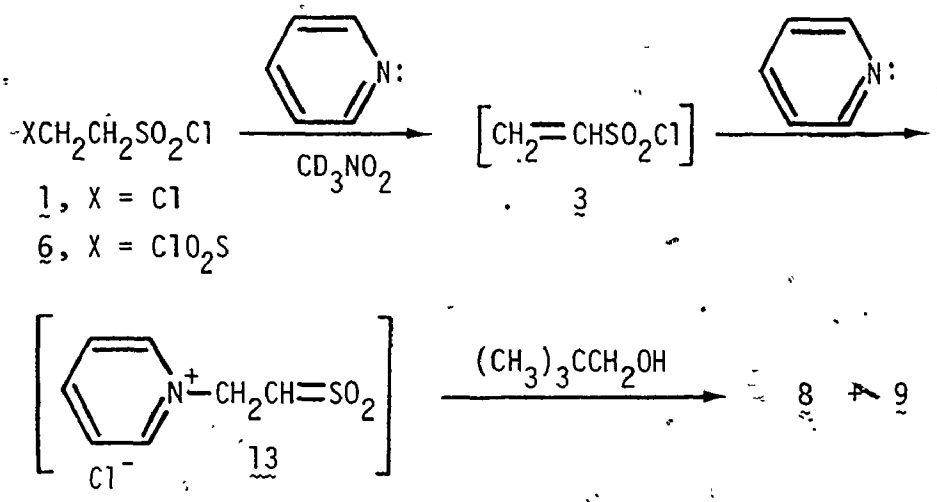
SCHEME 3.6



The observation of the same reaction products in the same relative proportions (within experimental error) for the reactions of

ethenesulfonyl chloride (3), 2-chloroethanesulfonyl chloride (1), and 1,2-ethanedisulfonyl chloride (6) with pyridine and neopentyl alcohol is consistent with a common reaction pathway for these compounds. This is shown in Scheme 3.7.

SCHEME 3.7

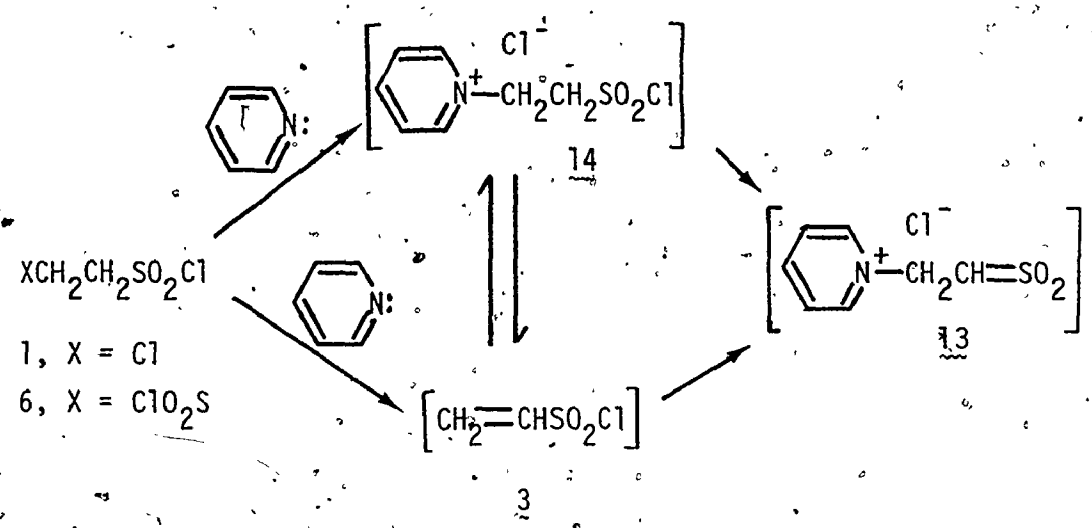


The elimination of the chlorosulfonyl group in the reaction of 6 with pyridine has some precedent in observations of earlier workers (4, 5,6) of this functionality as a leaving group. For example, Kohler (5) obtained large proportions of ethenesulfonate esters (acids) in the alcoholysis (hydrolysis) reactions of 6.

It should also be noted that the reaction of 2-chloroethanesulfonyl chloride (1) with either triethylamine or 2,6-lutidine is a preparative route (7) for ethenesulfonyl chloride (3).

The mechanism proposed for the generation of 8 and 9 from the sulfene (13) is more fully described in Scheme 2.3 (Chapter 2). Possible mechanisms by which the sulfene (13) may be generated in the reactions of 1 and 6 with pyridine are illustrated in Scheme 3.8.

SCHEME 3.8



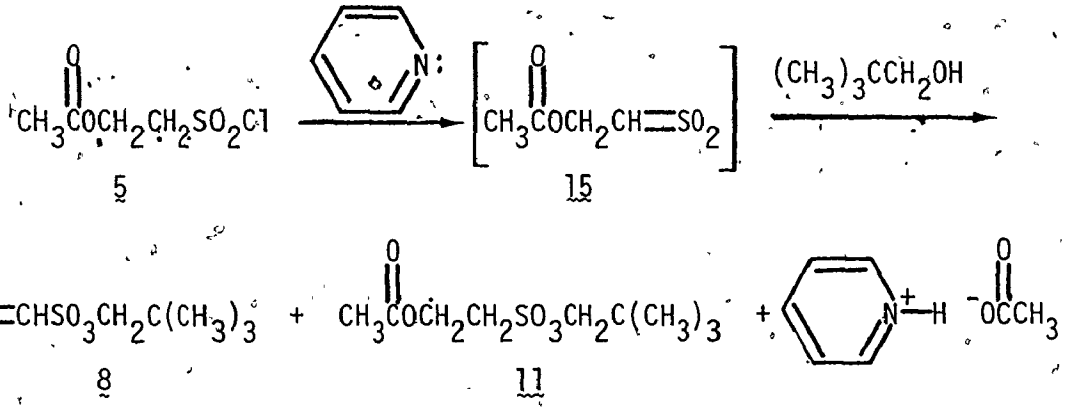
The generation of the pyridiniosulfonyl chloride (14) by direct (S_N2) substitution of 1 or 6 with pyridine is unlikely however, since neopentyl 2-chloroethanesulfonate (10) and neopentyl 2-acetoxyethanesulfonate (11) are unreactive towards pyridine under the reaction conditions. Therefore, the first step towards the generation of the sulfene (13) from 1 and 6 is probably the elimination of HX to produce ethenesulfonyl chloride (3). The pyridiniosulfonyl chloride (14) may be formed from ethenesulfonyl chloride (3) (a process excluded in an aqueous medium, Chapter 1), which then generates 13.

The low isolated yields of the ethenesulfonate esters reported in the reactions of 2-chloroethanesulfonyl chloride (1) and 2-bromoethanesulfonyl chloride (2) with pyridine and alcohols in CH_2Cl_2 (1), may be at least partly due to the generation of substantial amounts of the [2]-betylate in these reactions. The [2]betylate would not have been isolated under the workup conditions reported by Whitmore and Landau (1), but would probably have hydrolysed to generate the betaine and the alcohol.

From the results of these reactions one would predict that the reaction of 6 with a hindered base such as 2,6-lutidine would result in the formation (and observation) of ethenesulfonyl chloride (3), since 2,6-lutidine reacts with 3 only very slowly (see Chapter 1). This was indeed the observed result when 6 was treated with 2,6-lutidine in an n.m.r. tube at 37°. The characteristic peaks of 3 were immediately observed in the ^1H n.m.r. spectrum when 2,6-lutidine was added to a solution of 6 in $CDCl_3$.

For the reaction of 2-acetoxyethanesulfonyl chloride (5) with pyridine and neopentyl alcohol, the absence of [2]betylate (9) in the ^1H n.m.r. spectrum of the reaction mixture shows that ethenesulfonyl chloride (3) is not present as a reactive intermediate here. Therefore, the observed reaction products (8 and 11) are most likely formed by reaction of neopentyl alcohol with an intermediate 2-acetoxymethylsulfene (15), as shown in Scheme 3.9:

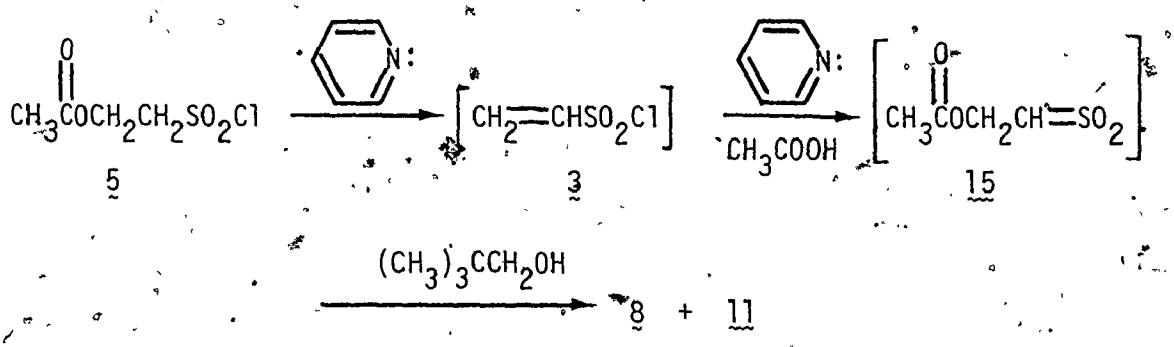
SCHEME 3.9



The possibility that 3 could be generated from 5, which could then react with acetic acid in a general base catalysed reaction to form 15

(as shown in Scheme 3.10) was excluded by a control experiment. Ethenesulfonyl chloride (3) was treated with an excess of pyridine and neopentyl alcohol in the presence of a small amount of acetic acid. Only neopentyl ethenesulfonate (8) and neopentyl [2]betylate (9) were observed (in relative proportions 72% and 28%, respectively). There was no sign of any neopentyl 2-acetoxyethanesulfonate (11) in the ^1H n.m.r. spectrum.

SCHEME 3.10

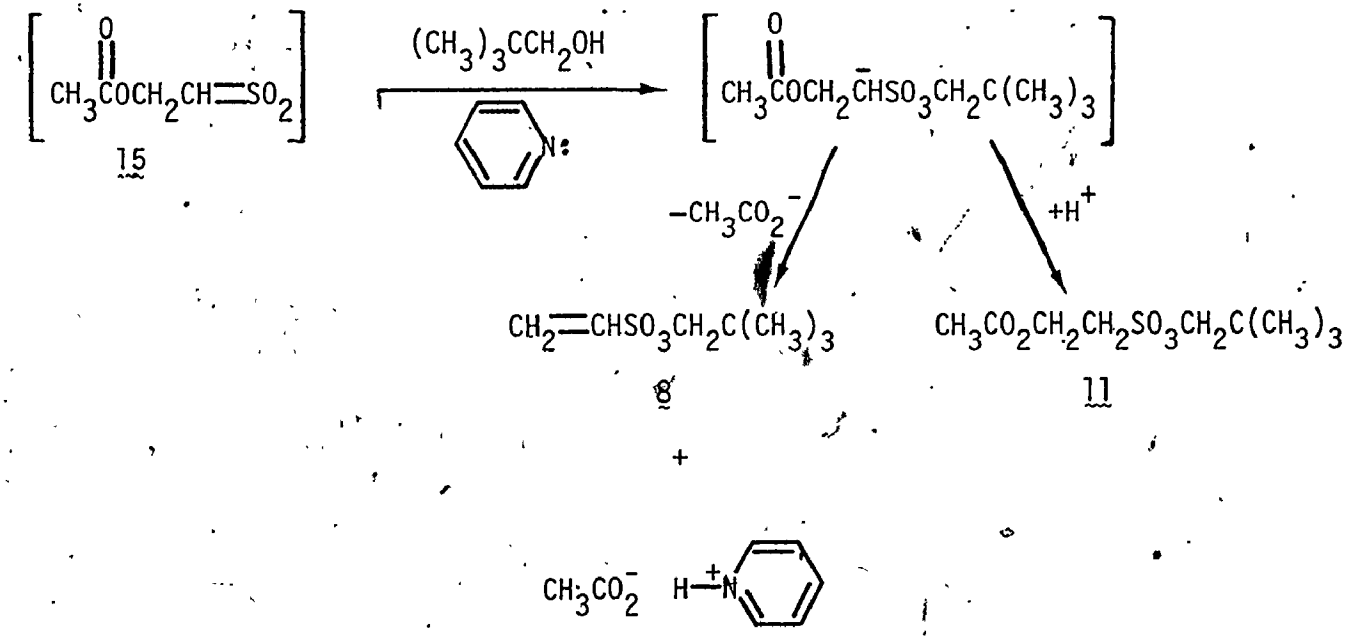


The generation of 8 and 11 from the sulfene (15) may occur by competing elimination and protonation reactions of a carbanion intermediate derived from sulfene (15), as shown in Scheme 3.11.

The reaction of 5 under these conditions appears to be similar to the reaction of N-[2-chlorosulfonylethyl] pyridinium chloride (14) (see Chapter 2). With both sulfonyl chlorides the intermediate which is initially formed is the substituted methylsulfene, which then reacts further to generate the mixture of neopentyl ethenesulfonate (8) and the substituted ethanesulfonate ester.

The relative proportion of 8 which is formed in the reactions of 5 and 14 under these conditions is 60% and 67%, respectively. While

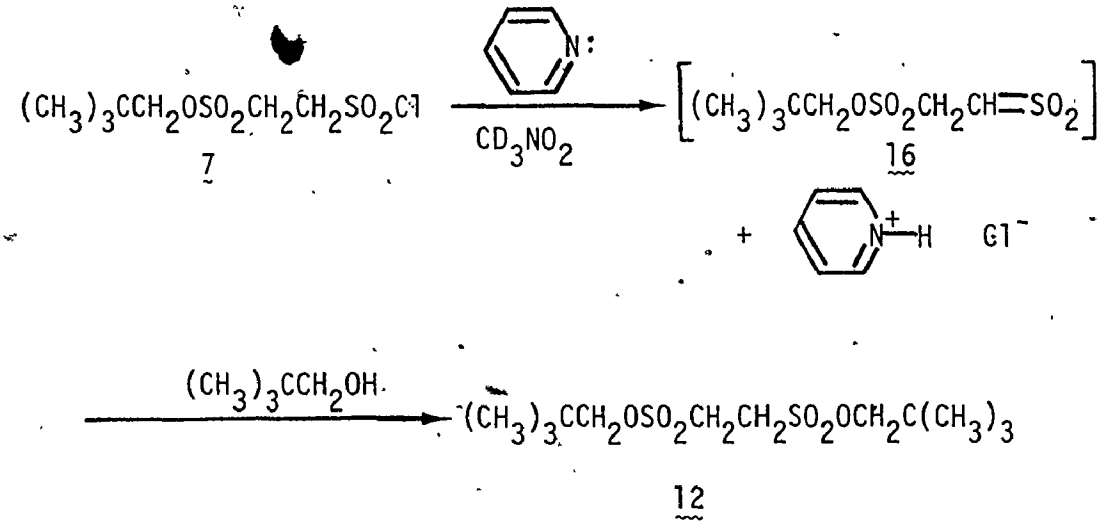
SCHEME 3.11


15
(CH3)3CCH2OH
−CH3CO2−
+H+
CH2=CHSO3CH2C(CH3)3
8
CH3CO2CH2CH2SO3CH2C(CH3)3
11
+
CH3CO2−

these relative proportions are very similar, the loss of the pyridine nucleofuge from a carbanion intermediate (as shown in Scheme 2.3) to form 8 may be faster than loss of acetate ion to form 8 as shown in Scheme 3.11. If the rates of protonation of the carbanion intermediates shown in these schemes were very similar, then the difference in nucleofugality between pyridine and acetate ion could be the source of the difference in the amount of 8 observed. In this context neutral leaving groups (such as N,N-dimethylaniline) have been highly ranked as nucleofuges in reversible ElcB reactions (8).

The reaction of neopentyl (2-chlorosulfonyl) ethanesulfonate (7) with pyridine and neopentyl alcohol resulted in the formation of dineopentyl-1,2-ethanedisulfonate (12) only. This reaction then apparently also proceeds by formation of a substituted methylsulfene (16) (as shown in Scheme 3.12), and not by formation of ethenesulfonyl chloride (3).

SCHEME 3.12



Trapping the sulfene (16) with neopentyl alcohol here yields only 12, with no neopentyl ethenesulfonate (8) formed by an elimination reaction. If trapping the sulfene (16) with the alcohol generates a carbanion intermediate, then based upon the results of King and Smith (6), the expulsion of $(CH_3)_3CCH_2OSO_2^-$ ion or its equivalent SO_2 and $(CH_3)_3CCH_2O^-$ ion (if this is a fragmentation reaction) might be expected to be a slow reaction. Therefore, protonation of the carbanion would generate (12) as the sole reaction product.

It is apparent that the reaction of 6 with pyridine results in formation of ethenesulfonyl chloride (3), whereas reaction of 7 with pyridine gives sulfene (16). This difference in reaction mechanism may be attributed to the more electron withdrawing power of the chlorosulfonyl group relative to the alkoxysulfonyl group, and the effect this difference has on the acidity of the hydrogen atoms α to these groups. The hydrogens α to the alkoxysulfonyl groups of 7 are not acidic enough to allow formation of neopentyl ethenesulfonate (8) by loss of the chlorosulfonyl group. Since chloride ion is a better nucleofuge than $(CH_3)_3CCH_2OSO_2^-$ ion, then sulfene (16) formation occurs when the α hydrogen is abstracted by the base, and no ethenesulfonyl chloride (3) is formed.

The mechanism by which the substituted ethanesulfonyl chlorides initially react with the tertiary amine in these elimination reactions may be either ElcB or E2 in nature. Whether a discrete carbanion or an incipient carbanion is involved in the initial elimination reaction, the stereochemistry of the transition state would most likely have an anti orientation between the carbanion (incipient carbanion) and the

nucleofuge which is leaving in the reaction.

In the first step, the formation of the carbon-carbon double bond might be expected to be a more exothermic reaction than the formation of the carbon-sulfur double bond in the sulfene (a rough value of 35 ± 5 kcal mol^{-1} for the π-bond energy of sulfene has been estimated (9), versus $\sim$65 kcal mol^{-1} for a carbon-carbon π-bond (10)). With a good leaving group at the beta carbon of the substituted ethanesulfonyl chloride, an E2-like transition state (with little or no carbanion character developed at the alpha carbon) to form ethenesulfonyl chloride (3) may be occurring. With a poorer leaving group at the beta carbon, more carbanion character may be built up at the α carbon, and loss of chloride ion to give the substituted sulfene occurs (ElcB or E2 reaction) instead.

3.3 Conclusions

The nature of the substituent present at the beta carbon of substituted ethanesulfonyl chlorides has considerable influence upon the mechanism of the elimination reactions of these compounds. 2-Chloroethanesulfonyl chloride (1) and 1,2-ethanedisulfonyl chloride (6) react with pyridine to initially form ethenesulfonyl chloride (3), whereas 2-acetoxyethanesulfonyl chloride (5), N-pyridinioethanesulfonyl chloride (14) and neopentyl 2-(chlorosulfonyl)ethanesulfonate (7) react by initially forming the substituted methylsulfene intermediate. Reactions of the sulfenes derived from 5 and 14, however, lead to partial loss of the acetoxy and pyridinio groups respectively to generate neopentyl ethenesulfonate (8).

3.4 Experimental

The general remarks given in the experimental section of Chapter 2 apply here also. 2-Acetoxyethanesulfonyl chloride (5) was prepared as described in Chapter 4. 2-Chloroethanesulfonyl chloride (1), was prepared as described in Chapter 1. Neopentyl 2-(chlorosulfonyl)ethanesulfonate (7) was prepared by the method of Aslam (2), ^{1}H n.m.r. (CD_3NO_2) δ: 1.12 (s, 9H), 3.89 (t, 2H), 4.06 (s, 2H), 4.35 (t, 2H). Ethane-1,2-disulfonyl chloride (6) was prepared according to the method of Saunders (11), and recrystallized from hexanes (m.p. 91°, lit. m.p. 91° (11); ^{1}H n.m.r. (CD_3NO_2) δ: 4.52 (s); i.r. (CH_2Cl_2) 2980 (w), 2920 (w), 1385 (vs), 1225 (w), 1180 (m), 1165 (s), 550 (m), 490 (m) cm^{-1}.

Preparation of Neopentyl 2-Chloroethanesulfonate (10)

2-Chloroethanesulfonyl chloride (1) (3.5 g, 2.16×10^{-2} mol) was combined with neopentyl alcohol (1.9 g, 2.16×10^{-2} mol) and methylene chloride (5 mL) at room temperature. After standing at 50° for 10 days the solvent was evaporated and the oily brown residue distilled under reduced pressure in a cold finger apparatus (0.5 mm Hg, oil bath temperature 120°) to yield a colorless oil (0.60 g, 15%); ^{1}H n.m.r. ($CDCl_3$) δ: 1.00 (s, 9H), 3.70 (m, 4H), 3.93 (s, 2H); ^{1}H n.m.r. (CD_3NO_2) δ: 1.02 (s, 9H), 3.62 (m, 2H), 3.92 (m, 2H), 3.96 (s, 2H); i.r. (neat) 2960 (m), 1355 (s), 1205 (s), 1170 (vs), 955 (s), 935 (s), 845 (m) cm^{-1}; Anal. calcd. for $C_7H_{15}ClO_3S$: C, 39.16; H, 7.04; Cl, 16.51; S, 14.93. Found: C, 39.31; H, 7.09; Cl, 16.42; S, 15.03.

Preparation of Dineopentyl-1,2-Ethanedisulfonate (12)

Neopentyl 2-(chlorosulfonyl)ethanesulfonate (7) (0.60 g, 2.15×10^{-3} mol) was dissolved in methylene chloride (25 mL) containing neopentyl alcohol (0.50 g, 5.5×10^{-3} mol) at room temperature. Pyridine (0.75 mL, 9.3×10^{-3} mol) was added, and the solution was allowed to stand for 18 hours. The yellow solution was extracted with water (1 × 30 mL), and the organic layer dried, filtered and evaporated to yield a yellowish solid (0.35 g, 50%). The solid was recrystallized from ethyl acetate/petroleum ether (60° - 80°), m.p. 150° - 152°; ^{1}H n.m.r. (CD_3NO_2) δ: 1.01 (s, 9H), 3.57 (s, 2H), 3.94 (s, 2H); i.r. (CH_2Cl_2) 3055 (w), 2955 (m), 2860 (w), 1465 (w), 1349 (s), 1215 (w), 1165 (s), 1149 (s), 938 (vs), 915 (s) cm^{-1}; Anal. calcd. for $C_{12}H_{26}O_6S_2$: C, 43.62; H, 7.93; S, 19.41; Found: C, 43.73; H, 8.10; S, 19.62.

Neopentyl 2-Acetoxyethanesulfonate (10)

A crude mixture of neopentyl ethenesulfonate (8) and neopentyl 2-acetoxyethanesulfonate (10) (obtained from a reaction of 2-acetoxyethanesulfonyl chloride (5) with neopentyl alcohol and triethylamine) was placed under reduced pressure (0.2 mm Hg, oil bath temperature 90°) to evaporate 8 (b.p. 62°, 0.02 mm Hg (2)). The colorless oily residue gave the following data: ^{1}H n.m.r. ($CDCl_3$) δ: 1.00 (s, 9H), 2.09 (s, 3H), 3.46 (t, 2H), 3.91 (s, 2H), 4.49 (t, 2H); (CD_3NO_2) δ: 1.01 (s, 9H), 2.08 (s, 3H), 3.63 (t, 2H), 3.95 (s, 2H), 4.57 (t, 2H); i.r. (neat) 2970 (m), 1750 (s), 1350 (s), 1240 (s), 1160 (s), 1030 (m), 955 (s), 840 (m) cm^{-1}; Anal. calcd. for $C_9H_{18}O_5S$: C, 45.36; H, 7.61; S, 13.46. Found: C, 45.41; H, 7.52; S, 13.31.

Reaction of 2-Chloroethanesulfonyl Chloride (1) with Neopentyl Alcohol and Pyridine-d_5 in Nitromethane-d_3 at 37°C

2-Chloroethanesulfonyl chloride (1) (0.023 g, 1.42×10^{-4} mol) was dissolved in nitromethane-d_3 (0.250 mL) containing neopentyl alcohol (0.023 g, 2.61×10^{-4} mol) and placed in an n.m.r. tube. Pyridine-d_5 (60 μL, 6.8×10^{-4} mol) was then injected into the solution. The ^1H n.m.r. spectrum was immediately obtained, and showed singlets at δ: 3.8, 4.0 with multiplets at 4.3, 5.3 and from 6.2 - 7.0 ppm. These absorptions indicated the presence of neopentyl ethenesulfonate (8) and neopentyl [2]betylate chloride (9), with no absorptions corresponding to neopentyl 2-chloroethanesulfonate (10) observed. The relative proportions of 8 and 9 were determined (by integration of the singlets at δ3.8, 4.0 ppm) to be 71% and 29%, respectively.

Reaction of Ethane-1,2-disulfonyl Chloride (6) with Pyridine and Neopentyl Alcohol in Nitromethane at 37°C

The sulfonyl chloride (6) (0.029 g, 1.28×10^{-4} mol) was dissolved in nitromethane-d_3 (0.400 mL) containing neopentyl alcohol (0.023 g, 2.6×10^{-4} mol) in an n.m.r. tube at 37°. Pyridine-d_5 (60 μL, 6.8×10^{-4} mol) was injected, the solution thoroughly mixed, and the ^1H n.m.r. spectrum obtained immediately. Neopentyl ethenesulfonate (8) and neopentyl [2]betylate (9) were the only two products observed; the relative proportions, determined as above, were 69% and 31% respectively.

Reaction of 2-Acetoxyethanesulfonyl Chloride (5) with Pyridine and Neopentyl Alcohol in Nitromethane-$\underline{d}_3$ at 37°C

2-Acetoxyethanesulfonyl chloride (5) (0.030 g, 1.61×10^{-4} mol) was dissolved in nitromethane-$\underline{d}_3$ (0.400 mL) containing neopentyl alcohol (0.024 g, 2.7×10^{-4} mol) in an n.m.r. tube at 37°. Pyridine-$\underline{d}_5$ (70 μL, 8.2×10^{-4} mol) was injected, the solution thoroughly mixed, and the ^{1}H n.m.r. spectrum obtained. Singlets were observed at δ: 2.1, 3.8, 3.9 ppm, a triplet at 3.7 and a multiplet from 6.2 - 7.0 ppm. This indicated the presence of neopentyl 2-acetoxyethanesulfonate (11) and neopentyl ethenesulfonate (8) in relative proportions (determined by integration of the singlets at 3.8, 3.9 ppm) 40% and 60%, respectively.

Reaction of Neopentyl 2-(Chlorosulfonyl)ethanesulfonate (7) with Pyridine-$\underline{d}_5$ and Neopentyl Alcohol at 37°C

The sulfonyl chloride (7) (0.029 g, 1.04×10^{-4} mol) was dissolved in nitromethane-$\underline{d}_3$ (0.400 mL) containing neopentyl alcohol (0.018 g, 2.04×10^{-4} mol) at 37°. Pyridine-$\underline{d}_5$ (0.050 mL, 5.8×10^{-4} mol) was injected and the solution thoroughly mixed. The ^{1}H n.m.r. spectrum of the reaction solution showed absorptions consistent with neopentyl 1,2-ethanedisulfonate (12), and no absorptions due to either neopentyl ethenesulfonate (8) or neopentyl[2]betylate (9) were observed. After a few minutes a colorless precipitate was observed. After several hours this precipitate was filtered (∿0.005 g). The ^{1}H n.m.r. spectrum ($CDCl_3$) of this material was identical to that of an authentic specimen of neopentyl ethanedisulfonate (12). The filtrate was dissolved in methylene chloride and the solvent evaporated to yield a colorless crystalline solid (∿0.035 g) whose ^{1}H n.m.r. spectrum ($CDCl_3$) indicated the presence

of 12 and a trace of neopentyl alcohol.

Reaction of Ethane-1,2-disulfonyl Chloride (6) with 2,6-Lutidine in Chloroform-d at 37°C

The sulfonyl chloride (6) (0.036 g, 1.59×10^{-4} mol) was dissolved in $CDCl_3$ (~0.5 mL) in an n.m.r. tube at 37°. 2,6-Lutidine (25 μL, 2.1×10^{-4} mol) was then injected and the solution mixed thoroughly. The ^1H n.m.r. spectrum was obtained immediately thereafter and exhibited absorptions characteristic of ethenesulfonyl chloride (3) and 2,6-lutidine, with no sign of 6. An authentic specimen of 3 was then added to the solution, with the resulting enhancement of the peaks ascribed to 3.

Control Experiment

Neopentyl 2-Acetoxyethanesulfonate (10) with Pyridine-d_5, Pyridinium Chloride and Neopentyl Alcohol

Neopentyl 2-acetoxyethanesulfonate (10) (0.030 g, 1.26×10^{-4} mol) was dissolved in nitromethane-d_3 (0.400 mL) containing neopentyl alcohol (0.018 g, 2.04×10^{-4} mol) in an n.m.r. tube at room temperature. Pyridine-d_5 (0.050 mL, 5.8×10^{-4} mol) was injected. After 14 hours the ^1H n.m.r. spectrum showed no observable reaction. Pyridinium-d_5 chloride (0.020 g, 1.65×10^{-4} mol) was then added. After 4 more hours at room temperature the ^1H n.m.r. spectrum still showed that neopentyl 2-acetoxyethanesulfonate (10) was completely unchanged.

Control Experiment

Neopentyl 2-Chloroethanesulfonate (10) with Pyridine-d_5 and Neopentyl Alcohol in Nitromethane

Neopentyl 2-chloroethanesulfonate (10) (0.025 g, 1.16×10^{-4} mol) was dissolved in nitromethane-d_3 (0.400 mL) containing neopentyl alcohol (0.016 g, 1.81×10^{-4} mol) in an n.m.r. tube. To this solution pyridine-d_5 (0.050 mL, 5.8×10^{-4} mol) was added. After 90 minutes at room temperature the ^{1}H n.m.r. spectrum of the solution showed 10 was unchanged. After 5 days at room temperature a trace amount (<5%) of neopentyl ethenesulfonate (8) was observed in the ^{1}H n.m.r. spectrum, but no peaks corresponding to neopentyl [2]betylate (9) were observed.

Control Experiment

Reaction of Ethenesulfonyl Chloride (3) with Pyridine and Neopentyl Alcohol in Nitromethane Containing Acetic Acid at 37°C

The sulfonyl chloride (3) (0.038 g, 3.0×10^{-4} mol) was dissolved in nitromethane-d_3 (0.400 mL) containing neopentyl alcohol (0.050 g, 5.7×10^{-4} mol) and acetic acid (6 μL, 1.0×10^{-4} mol, glacial acetic acid dried by addition of 5% acetic anhydride) at 37°. Pyridine-d_5 (0.100 mL, 1.2×10^{-3} mol) was injected, and the ^{1}H n.m.r. spectrum obtained. Neopentyl ethenesulfonate (8) (72%) and neopentyl [2]betylate (9) (28%) were the only observed products.

CHAPTER 4

SYNTHESIS AND CHEMISTRY OF 2-HYDROXYETHANESULFONYL CHLORIDE

4.1 Introduction

Hydroxyalkanesulfonyl chlorides (the general structure of α,ω-hydroxyalkanesulfonyl chlorides is shown below) are molecules incorporating two highly reactive functional groups. These groups are capable of reacting with a wide variety of reagents, and may react with each other either intermolecularly or intramolecularly as well. For these reasons they could potentially display some interesting and varied

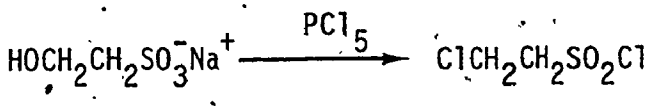
$$HO(CH_2)_nSO_2Cl$$

chemistry. A hydroxyalkanesulfonyl chloride of particular interest at this time is 2-hydroxyethanesulfonyl chloride (1), a hitherto unknown compound. The synthesis of this particular sulfonyl chloride was

$$HOCH_2CH_2SO_2Cl \qquad \left[HOCH_2CH{=}SO_2\right]$$

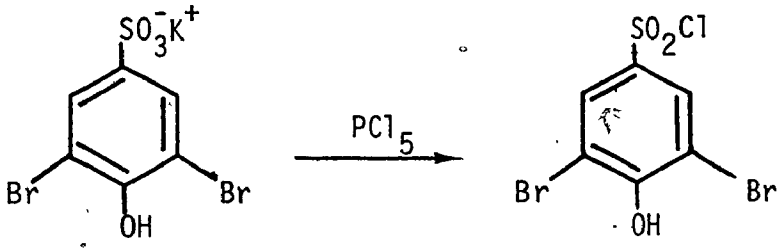
1 2

desirable because this compound (and a related species, 2-hydroxymethylsulfene (2)) were possible reactive intermediates in the uncatalysed hydrolysis reactions of ethenesulfonyl chloride (3) (as discussed in Chapter 1). Because of the reactivity of the alcohol functionality, these unusual alkanesulfonyl chlorides had not previously been isolated. For example, treatment of sodium 2-hydroxyethanesulfonate (sodium isethionate) (4) with phosphorus pentachloride or thionyl chloride (with or without added dimethylformamide catalyst) yields only 2-chloroethanesulfonyl chloride (5) (1).



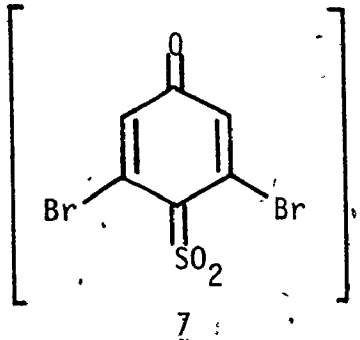
4 5

A few hydroxyarenesulfonyl chlorides have been unambiguously characterized, however. The first of these compounds was 3,5-dibromo-4-hydroxybenzenesulfonyl chloride (6), prepared by Zincke and Glahn in 1907 (2).



6

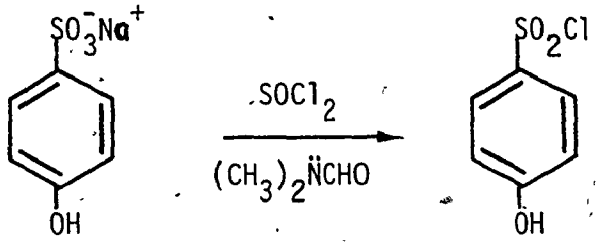
When 6 was treated with potassium acetate solution (3), a bright yellow color was observed which slowly faded away. The authors proposed that the yellow color was due to a "quinoid sulfene" (7), and that the product isolated from the reaction was in fact a dimer of 7.



7

Recent work by Williams and co-workers (6) with hydroxyarenesulfonate esters makes it very likely that the original suggestion by Zincke for the "quinoid sulfene" (7) intermediate in these reactions is accurate.

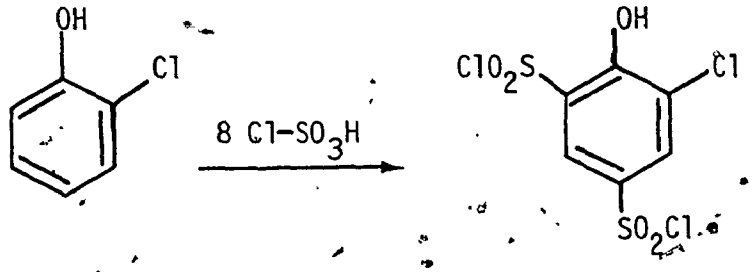
During the reinvestigation of Zincke's work, Hall also prepared several other 3,5-disubstituted 4-hydroxybenzenesulfonyl chlorides. However, it remained for Campbell and Hill (7) in 1972 to prepare the parent compound, 4-hydroxybenzenesulfonyl chloride (9). They suggested that this compound "had apparently resisted synthesis because of the



9

reactive, unhindered phenolic group." Very little chemistry was done with this sulfonyl chloride (9), except to polymerize it into a "high molecular weight polymer" under some reaction conditions (8).

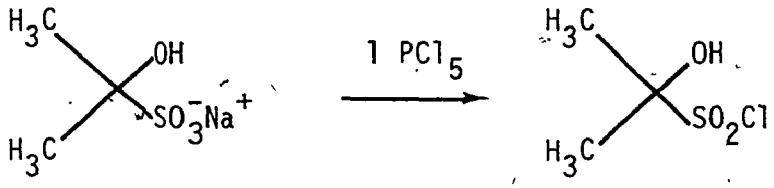
Very recently a series of isomeric chlorohydroxybenzenesulfonyl chlorides were prepared (9), including an unusual compound, 5-chloro-4-hydroxybenzene-1,3-bis-sulfonyl chloride (10) in 59% yield.



10

This compound and other similar sulfonyl chlorides were treated with 1° and 2° amines, hydrazines and sodium azide to generate sulfonamides, sulfonhydrazides and sulfonyl azides, respectively.

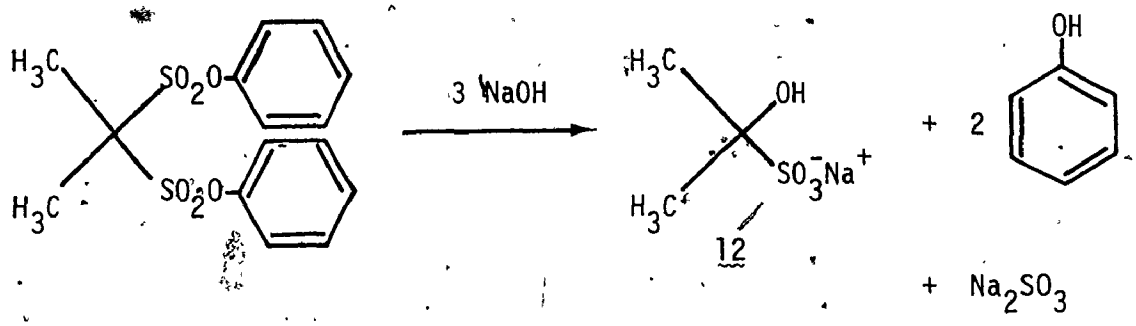
The only report of the synthesis of an alkanesulfonyl chloride bearing a hydroxyl group is that of Schroeter (10) who asserted that he had prepared 2-hydroxy-2-propanesulfonylchloride (11) from sodium 2-hydroxy-2-propanesulfonate (12). A material believed to be the N-



12 11

ethylsulfonanilide of 11 was also described in the same paper. The structure of the proposed starting material 12 (prepared by the route shown in Scheme 4.1) was disputed by Raschig and Prahl (11), who prepared an authentic specimen of the bisulfite adduct of acetone. Raschig's structure for the bisulfite adduct has since been proved correct.

SCHEME 4.1



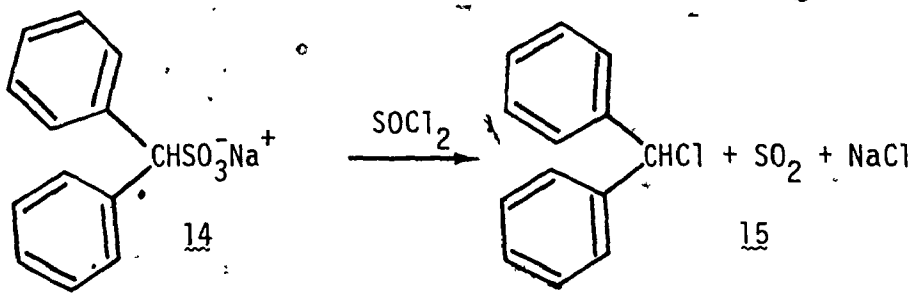
Our interest in the preparation of 2-hydroxyethanesulfonyl chloride (1) was given added importance when, during the course of the efforts towards the synthesis of 1, it became apparent that the work of Hesse, Reichold and Majumdar (12) with barium 2-hydroxyethanesulfinate (13) was incorrect (see Appendix 3).

$$(HOCH_2CH_2SO_2^-)_2Ba^{2+}$$

13

It had been hoped that the aqueous chlorination of this sulfinate salt (13) (a useful method for the synthesis of sulfonyl chlorides is the chlorination of sulfinic acids or their salts (13)) would have readily furnished the desired sulfonyl chloride (1). However, an attempt to prepare 13 by the literature method proved to be unsuccessful.

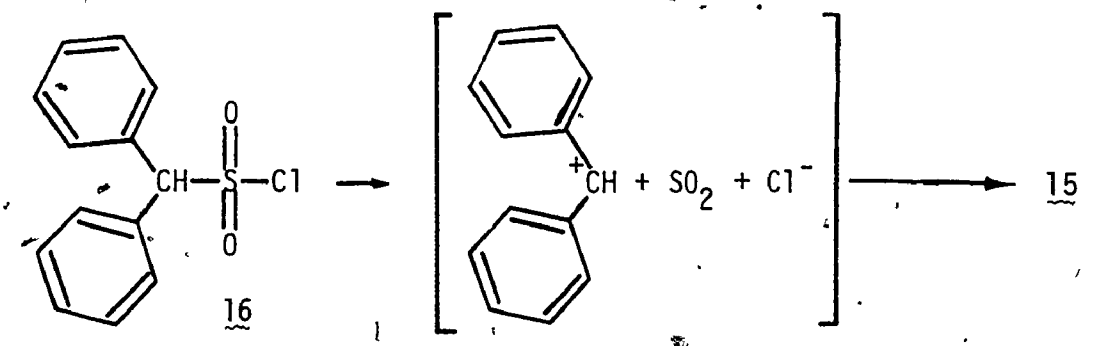
Regarding the question of the ease of synthesis of an alkanesulfonyl chloride bearing a neighboring hydroxyl group, several authors have reported difficulties in obtaining sulfonyl chlorides in instances where reasonably stable cations may form during the course of the reaction. For example, treatment of sodium diphenylmethanesulfonate (14) with thionyl chloride resulted in the formation of benzhydryl chloride (15) and not the expected product, diphenylmethanesulfonyl chloride (16) (14).



14 15

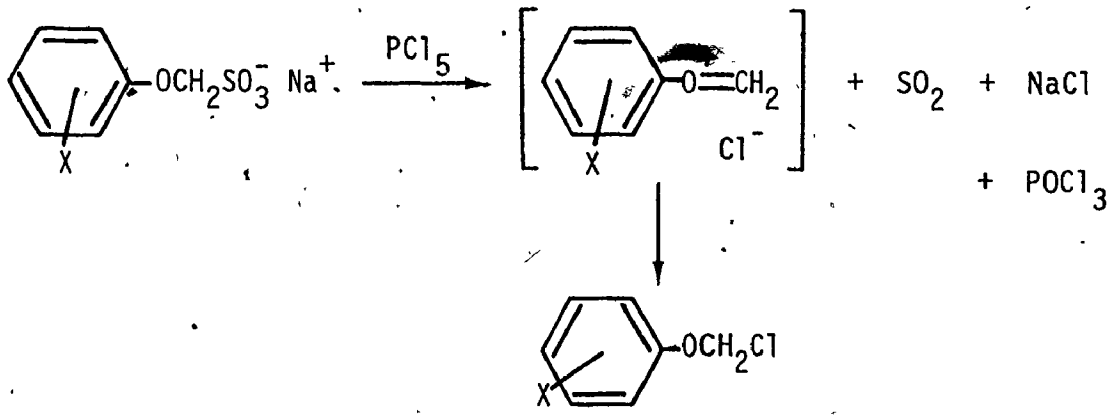
Assuming that the desired sulfonyl chloride (16) was indeed initially formed (which need not necessarily be true), one possible mechanism* for generating the observed products is that shown in Scheme 4.2.

SCHEME 4.2



Another apparently related reaction (15) involves the chlorination of aryloxymethanesulfonic acids or their sodium or potassium salts with phosphorus pentachloride. The reaction products are the aryloxymethyl chloride and sulfur dioxide, a reaction which most likely proceeds via an oxonium ion intermediate, as shown in Scheme 4.3.

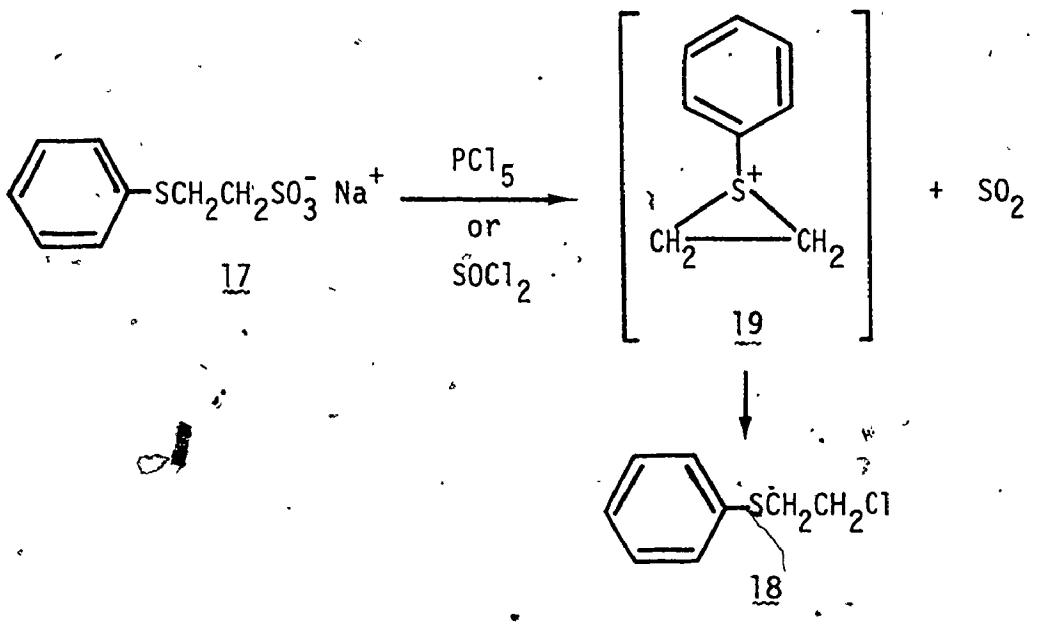
SCHEME 4.3



*A mechanism similar to the one shown in Scheme 4.2 has been suggested by King and Aslam (14) to explain the isolation of an ether in the reaction of diphenyldiazomethane with sulfur dioxide and 2,4-dinitrophenol.

There is even evidence which suggests that neighboring group participation may be occurring in the attempted synthesis of some β-substituted ethanesulfonyl chlorides (16). When sodium 2-phenylthioethanesulfonate (17) was treated with phosphorus pentachloride or thionyl chloride, the isolated product was 2-phenylthioethyl chloride (18), probably arising from an intermediate episulfonium ion (19) as shown in Scheme 4.4.

SCHEME 4.4



In view of the difficulty associated with the synthesis of a sulfonyl chloride which may easily generate a reasonably stable cation, the reported isolation of 11 instead of acetone from the apparent chlorination of 12 is surprising indeed. The reinvestigation of Schroeter's work by modern methods would seem to be required.

There are many available methods for the synthesis of a sulfonyl chloride from a wide variety of precursors (13,17,18). One of the oldest preparative routes to sulfonyl chlorides has been the chlorination of the corresponding sulfonic acid or its sodium or potassium

salt using thionyl chloride or phosphorus pentachloride (19).

$$R\text{—}SO_3H \xrightarrow{PCl_5} RSO_2Cl + HCl + POCl_3$$

This synthetic route to sulfonyl chlorides is still much used today and gives reasonable yields of the desired product. Another common route to sulfonyl chlorides was discovered in the 1930's by Douglass and Johnson (20), and involves the oxidative aqueous chlorination of a thiol to the corresponding sulfonyl chloride.

$$RSH \xrightarrow[H_2O]{Cl_2} RSO_2Cl$$

This route has remained extremely useful for the general synthesis of sulfonyl chlorides, although the oxidative chlorination procedure is not limited to thiols. Many compounds such as sulfides and isothiuronium salts may be oxidatively chlorinated to sulfonyl chlorides in good yield (18,21).

In the 1960's Goethals and Verzele (22) discovered that the aqueous chlorination of ω-hydroxyalkanethiols resulted in the formation of ω-chloroalkanesulfonyl chlorides or sultones, or a mixture of both compounds.

$$HO(CH_2)_nSH \xrightarrow[H_2O]{Cl_2} Cl(CH_2)_nSO_2Cl + (CH_2)_n\text{—}SO_2 \quad (O)$$

$n = 3\text{-}6$

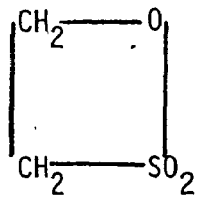
They observed that for some hydroxyalkanethiols (n = 5,6) the sulfonyl chloride was the only isolated product of the aqueous chlorination reaction. No evidence for the formation of any ω-hydroxyalkanesulfonyl

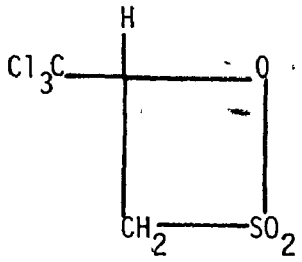
chloride has ever been reported for the aqueous chlorination of hydroxyalkanethiols, nor was such a species even postulated as a reactive intermediate in these reactions.

Amongst the best applications of this procedure in the preparation of a sulfonyl chloride was the synthesis of 2-chloroethanesulfonyl chloride (5) from 2-mercaptoethanol (20) in 94% yield using a two phase system for the chlorination (23).

$$HOCH_2CH_2SH \xrightarrow[H_2O/ClCH_2CH_2Cl]{Cl_2} ClCH_2CH_2SO_2Cl$$

In this reaction neither the unsubstituted β-sultone (21) nor 2-hydroxyethanesulfonyl chloride (1) was reported. While the parent β-sultone (21) has so far eluded all attempts to isolate it, several other substituted β-sultones have been characterized (24-27). These compounds usually have at least one electron withdrawing group present on the ring.





21

This Chapter describes the preparation of what may well prove to be the simplest possible hydroxyalkanesulfonyl chloride, 2-hydroxyethanesulfonyl chloride (1). Some of the chemistry of this unusual sulfonyl chloride will also be presented and discussed.

4.2 Results and Discussion

(a) Preparation and Characterization of 2-Hydroxyethanesulfonyl Chloride (1)

Following the same general procedure as first described by Douglass and Johnson (20), chlorine gas was rapidly bubbled into a cooled aqueous solution of 2-mercaptoethanol (20) with stirring for 10 minutes (initial and final reaction temperatures were approximately 3° and 40°C, respectively). After extraction of the solution with methylene chloride a colorless syrup was obtained in 20 to 30% yield, which was subsequently established to be 2-hydroxyethanesulfonyl chloride (1) on the basis of its physical and chemical properties. In these aqueous chlorinations,

$$\underset{\underline{20}}{HOCH_2CH_2SH} \xrightarrow[H_2O]{Cl_2} \underset{\underline{1}}{HOCH_2CH_2SO_2Cl} + \underset{\underline{5}}{ClCH_2CH_2SO_2Cl}$$

significant amounts of a co-product, 2-chloroethanesulfonyl chloride (5), were produced (as determined by the ^1H n.m.r. spectrum of the crude reaction product). Pure 1 was obtained either by first extracting with benzene to remove 5 followed by extraction with methylene chloride, or by repeated trituration of the crude mixture (obtained by extraction only with methylene chloride) with cyclohexane to remove 5. If the aqueous chlorination of 20 was performed for periods of time shorter than 10 minutes, or if the rate of addition of chlorine to the cooled solution was not rapid, then little or none of 1 was isolated.

The sulfonyl chloride (1) gave satisfactory elemental analysis and exhibited infrared absorptions (neat) indicative of a sulfonyl

chloride group as well as a free and hydrogen bonded hydroxyl group (3550, 3370, 1365, 1165 cm^{-1}). The ^1H n.m.r. spectrum ($CDCl_3$), Figure 4.1, displayed a symmetrical pattern of perturbed triplets characteristic of an AA'BB' system (4H, central peaks at δ3.98 and 4.28 ppm) plus a singlet (1H) at δ2.8 which was found to be exchangeable with D_2O. The ^{13}C n.m.r. spectrum ($CDCl_3$) displayed two singlets, at δ56.9 and 67.6 ppm respectively.

A neat sample of 1 was found to be stable at room temperature for several days, whereas a chloroform solution was unchanged even after 3 months. The slow decomposition of a neat sample of 1 was not an unexpected result since alkanesulfonyl chlorides have been shown to react slowly with primary alcohols at room temperature (28).

Treatment of a neat sample of 1 with excess acetyl chloride resulted in an 88% yield (after distillation) of 2-acetoxyethanesulfonyl chloride (22), identified by comparison with a sample prepared by a known route (19).

$$HOCH_2CH_2SO_2Cl \xrightarrow{CH_3\overset{\overset{O}{\|}}{C}Cl} CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_2SO_2Cl + HCl$$

1 22

As part of the investigation of the properties of 2-hydroxyethanesulfonyl chloride (1), several related derivatives of this compound were prepared using well established chemical procedures.

The sulfonyl chloride (1) was treated with an aqueous solution of sodium sulfite, followed by acidification with conc. H_2SO_4 at 0° to give, after continuous extraction with ether, 2-hydroxyethanesulfinic acid (23).

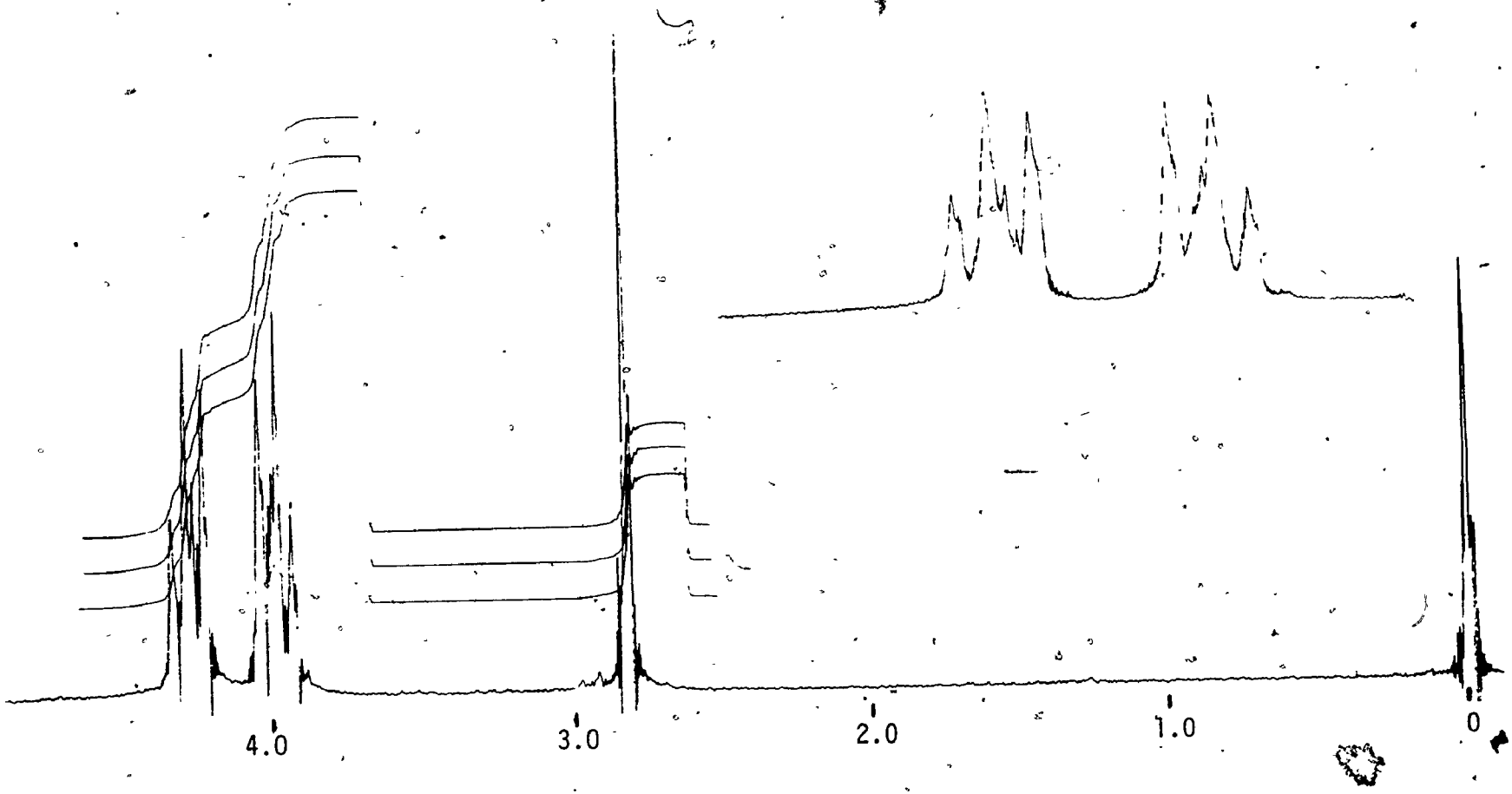


FIGURE 4.1 ^{1}H n.m.r. Spectrum ($CDCl_3$) of 2-Hydroxyethanesulfonyl Chloride

sweep width 500 Hz.
insert: region 3.7 - 4.5 ppm, sweep width 100 Hz.

$$HOCH_2CH_2SO_2Cl \xrightarrow[2)\ H_2SO_4]{1)\ Na_2SO_3} HOCH_2CH_2SO_2H$$

1 23

This sulfinic acid (23) was identified by its ^1H n.m.r. (D_2O) and infrared (neat) spectra, as well as a pK_a determination. The apparent pK_a was determined to be 2.68, a value close to those reported (29) for several aliphatic sulfinic acids. The acid (23) was easily converted back to the sulfonyl chloride (1) by passing chlorine into a D_2O solution of 23.

$$DOCH_2CH_2SO_2D \xrightarrow[D_2O]{Cl_2} DOCH_2CH_2SO_2Cl$$

23a 1a

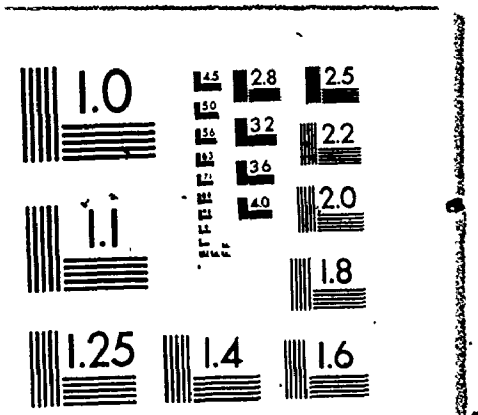
In separate experiments the sulfinic acid (23) was treated with aqueous solutions of sodium hydroxide and barium hydroxide to produce sodium 2-hydroxyethanesulfinate (24) and barium 2-hydroxyethanesulfinate (13), respectively.

$$HOCH_2CH_2SO_2^-\ Na^+ \xleftarrow{NaOH} HOCH_2CH_2SO_2H \xrightarrow{Ba(OH)_2} (HOCH_2CH_2SO_2^-)Ba^{2+}$$

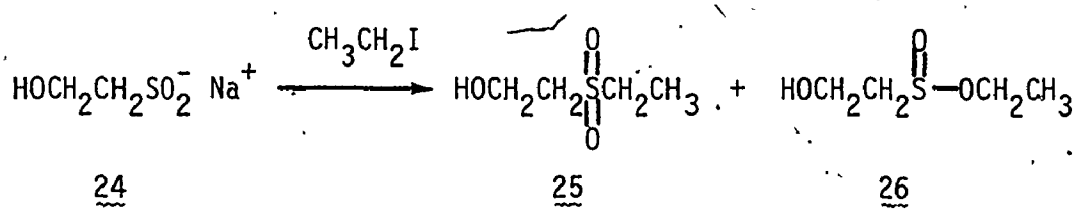
24 23 13

The barium salt (13) was identified by elemental analysis, ^1H n.m.r., i.r. spectra, and 24 was identified by its ^1H n.m.r., i.r. spectra. The chemistry of the barium salt (13) will be discussed in Appendix 3.

The sodium sulfinate (24) was alkylated with ethyl iodide to yield a small amount (15%) of ethyl 2-hydroxyethylsulfone (25). Sulfinate anions have been well-established as ambident nucleophiles (30), so that



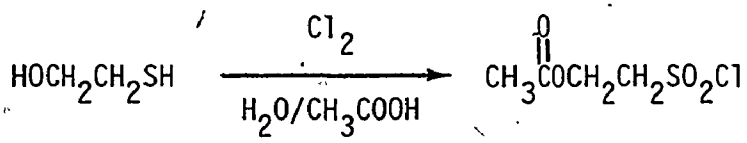
the crude reaction mixture may have contained some ethyl 2-hydroxyethyl sulfinate (26) along with the sulfone (25). However, the sulfinate ester (26) was not isolated from this reaction.



24 25 26

These reactions provided further evidence for the assigned structure of this unusual sulfonyl chloride (1).

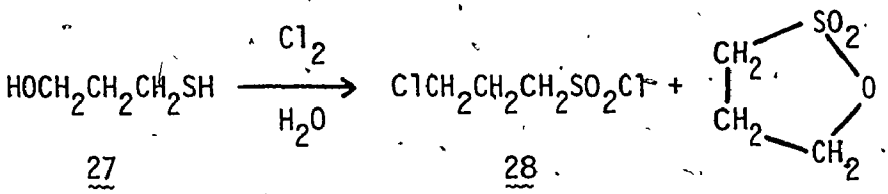
When the chlorination of 2-mercaptoethanol (20) was performed in a 1:1 mixture of water and acetic acid over 30 minutes the product, in 30% yield after distillation, was identified as the β-acetoxysulfonyl chloride (22). The yield of this reaction was not optimized, and



20 22

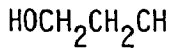
therefore remained lower than the overall yield in the literature (70%) (19,31) for the preparation of 22 from isethionate anion (4).

As a slight digression from the main focus of this work, 3-mercaptopropanol (27) was treated with aqueous chlorine under conditions similar to the oxidation of 20. The products of this reaction were investigated by ^{1}H n.m.r. spectroscopy and identified (by comparison with spectra of authentic specimens) as an equimolar mixture of 3-chloro-1-propanesulfonyl chloride (28) and 1,3-propanesultone (29), each in 24% yield.

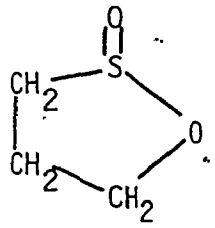


27 28 29

There were no absorptions in the ^1H n.m.r. spectrum of the reaction products which could be attributed to either 3-hydroxy-1-propanesulfonyl chloride (30) or 1,3-propanesultine (31).



30



31

To determine whether the sultine (31) was a reactive intermediate in the aqueous chlorination of the hydroxythiol (27), an authentic sample of the γ-sultine (31) was prepared (32) and chlorinated in a similar manner. The ^1H n.m.r. spectrum of the reaction products showed approximately a 6:1 ratio of the sultone (29) and the sulfonyl chloride (28). This result indicated that the γ-sultine (31) may be a reactive intermediate in the chlorination of 3-mercaptopropanol (27). The mechanism of these aqueous chlorinations of hydroxythiols was not investigated any further at this point.

(b) Chemistry of 2-Hydroxyethanesulfonyl Chloride (1)

(i) Solvolysis of 1 in Water and Deuterium Oxide at 25.0°C

The sulfonyl chloride (1) was solvolysed in water and D_2O at 25.0°C in the presence of varying initial concentrations of potassium chloride. These reactions were performed at several pH values using the pH stat method described in Chapter 1. In all of these solvolyses the major products were determined (by comparison with ^1H n.m.r. spectra of authentic specimens) to be 2-hydroxyethanesulfonate (isethionate) anion (4) and 2-chloroethanesulfonate anion (32), with traces of ethenesulfonate anion (34) observed at pH 11.

$$\underset{1}{HOCH_2CH_2SO_2Cl} \xrightarrow{H_2O} \underset{4}{HOCH_2CH_2SO_3^-} + \underset{32}{ClCH_2CH_2SO_3^-} + \underset{33}{CH_2{=}CHSO_3^-}$$

For the solvolyses performed in D_2O there was no evidence of deuterium incorporation in any of the products. The relative proportions of the observed products in these solvolyses are given in Table 4.1. A control experiment confirmed the stability of 4 and 32 under the solvolysis conditions.

From the results of the solvolyses performed in D_2O (no incorporation of deuterium into 4) it is evident that 2-hydroxymethylsulfene (2) is not an intermediate in these reactions, since the presence of 2 would have generated α monodeuterated 4 (Scheme 4.5).

TABLE 4.1

Products of the Solvolysis of 2-Hydroxyethanesulfonyl Chloride (1) in Water and Deuterium Oxide at 25.0°C

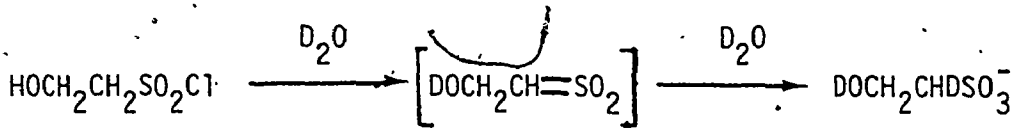
Solvent	pH	KCl M	$[S]_0$M(b)	Relative Proportions of Products(a)		
				$HOCH_2CH_2SO_3^-$ (4)	$ClCH_2CH_2SO_3^-$ (32)	$CH_2{=}CHSO_3^-$ (33)
H_2O	4.0	0	2.0×10^{-2}	87%	7%	< 1%(c)
H_2O	4.0	0.1	1.5×10^{-2}	80	20	< 1
H_2O	4.0	0.5	2.4×10^{-2}	50	50	< 1
H_2O	11.0	0	2.0×10^{-2}	76	7	1(c)
H_2O	11.0	0.1	1.5×10^{-2}	76	22	< 1(c)
D_2O	3.0	0	4.2×10^{-3}	86	14	< 1
D_2O	11.0	0	4.2×10^{-3}	90	9	1

(a) Relative proportions determined by integration of the ^1H n.m.r. spectrum (D_2O) of the crude reaction products.

(b) $[S]_0$ is the initial concentration of the sulfonyl chloride (1).

(c) The remainder of the reactions products was unidentified.

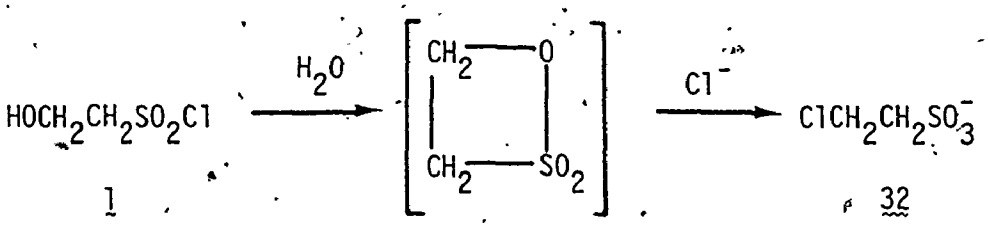
SCHEME 4.5



1 2 4

The significant increase in the relative proportion of 2-chloroethanesulfonate anion (32) with increasing initial concentrations of potassium chloride in these solvolyses, suggests that the chloride ion is effectively trapping a reactive intermediate. These results are consistent with the generation of a reactive β-sultone (21) intermediate from 1, followed by a rapid ring cleavage reaction by chloride ion to generate 33, as shown in Scheme 4.6.

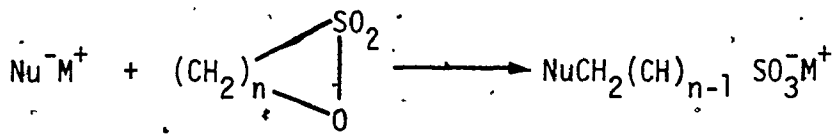
SCHEME 4.6



1 21 32

Sultones are cyclic sulfonate esters and have been shown to be quite reactive towards nucleophiles leading to ring opened substitution products, usually by way of the cleavage of the carbon-oxygen bond and not the sulfur-ring oxygen bond (27,33). Therefore the products of these ring opening reactions are ω-substituted alkanesulfonate salts, as shown in Scheme 4.7.

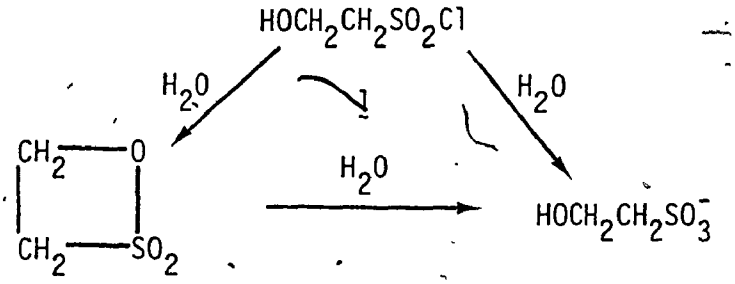
SCHEME 4.7



The reaction of chloride ion with the β-sultone (21) may be a specific example of the general behavior of sultones in the presence of a nucleophile.

The isethionate anion (4) observed in the solvolysis reaction of 1 may have been derived either by conventional nucleophilic attack by water at the sulfonyl group of 1, or from the β-sultone (21) or by both mechanisms. These routes are shown in Scheme 4.8.

SCHEME 4.8

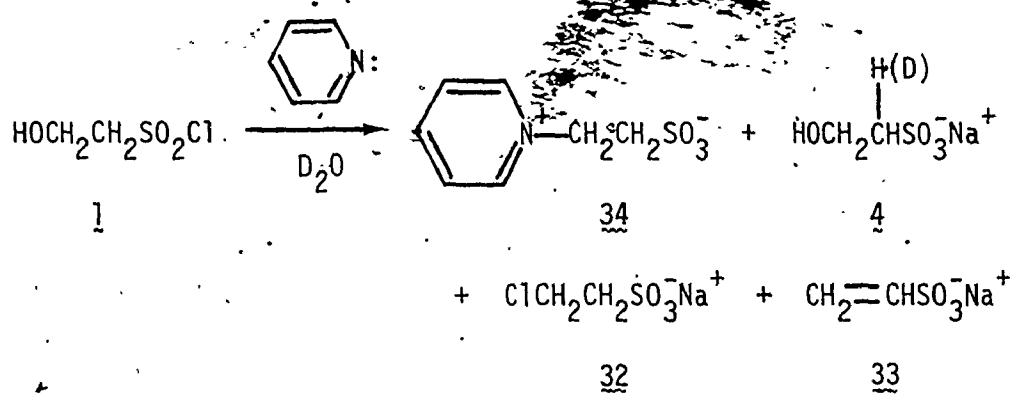


In principle ^{18}O labelling experiments could be helpful in establishing the mechanism by which the sulfonyl chloride (1) is solvolysed to 4. However, in the absence of further experiments, no conclusions may be drawn concerning the relative ease of these two mechanisms. It is very likely that at least some of 4 is generated by attack of water on 21 at low chloride ion concentrations.

(ii) Reaction of 2-Hydroxyethanesulfonyl Chloride (1) with Pyridine in Deuterium Oxide at 25.0°C

The sulfonyl chloride (1) was treated with excess pyridine in D_2O at apparent pH 6.0 and 25.0°C for 30 minutes using the pH-stat apparatus. After adjusting the pH to 7.5, the excess pyridine was extracted with ether. Evaporation of the aqueous layer gave a colorless solid whose ^1H n.m.r. spectrum (D_2O) indicated the presence of pyridine betaine (34), sodium isethionate-1-d (4) and sodium 2-chloroethanesulfonate (32), with a trace of sodium ethenesulfonate (33), as shown in Scheme 4.9. The products were identified by comparison with ^1H n.m.r. spectra of authentic specimens, and a control experiment demonstrated that the

SCHEME 4.9



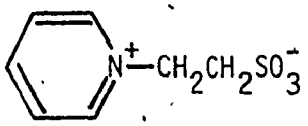
1 34 4 32 33

products were stable under the reaction conditions. The relative proportions of the products in the reaction mixture are given in Table 4.2.

Only sodium isethionate (4) was observed to have incorporated any deuterium, and it was estimated (by ^1H n.m.r. integration of the absorptions at δ: 3.12, 3.90 ppm) to be ≥50% monodeuterated at the α carbon. The observed deuterium pattern in the reaction products is consistent with the hypothesis that the pyridine betaine (34), sodium

TABLE 4.2

Products of Reaction of 2-Hydroxyethanesulfonyl Chloride (1) with Pyridine in Deuterium Oxide at 25.0°C

Product		Relative Proportion of Products (%)
	(34)	57
$HOCH_2\underset{\underset{H(D)}{|}}{C}HSO_3^-$	(4)	33
$ClCH_2CH_2SO_3^-$	(32)	7
$CH_2{=}CHSO_3^-$	(33)	3

2-chloroethanesulfonate (32) and undeuterated* isethionate (4) were derived by ring cleavage reactions of the intermediate β-sultone (21) with pyridine, chloride ion and water respectively. The monodeuterated isethionate (4) evidently arose by trapping the intermediate 2-hydroxymethylsulfene (2) with D_2O. These mechanisms are illustrated in Scheme 4.10.

The trace of ethenesulfonate anion (33) may have been generated either from 2 or 21, but it is evident that the intermediate hydroxymethylsulfene (2) does not generate large amounts of 33 under these reaction conditions.

With the chemistry of 1 and 2 in an aqueous system now reasonably well established, several questions regarding the possible intermediacy of 1 and 2 in the hydrolysis reactions of ethenesulfonyl chloride (3) (discussed in Chapter 1) may now be resolved. The lack of any ethenesulfonate anion (33) product in the hydrolysis reactions of the sulfonyl chloride (1) at low pH values eliminates 1 as a possible source of 33 in the hydrolysis reactions of ethenesulfonyl chloride (3). The absence of a significant amount of 2-chloroethanesulfonate anion (32) in the products of the hydrolysis of 3 at low pH values in 0.5 M potassium chloride (compared with a 1:1 ratio of 4:32 in the hydrolysis of 1 under the same conditions) eliminates the possibility of 1 as a precursor of isethionate anion (4) in the hydrolyses of 3.

Since 2-hydroxyethanesulfonyl chloride (1) is not an intermediate in the hydrolysis reactions of 3 in 0.5 M potassium chloride solution

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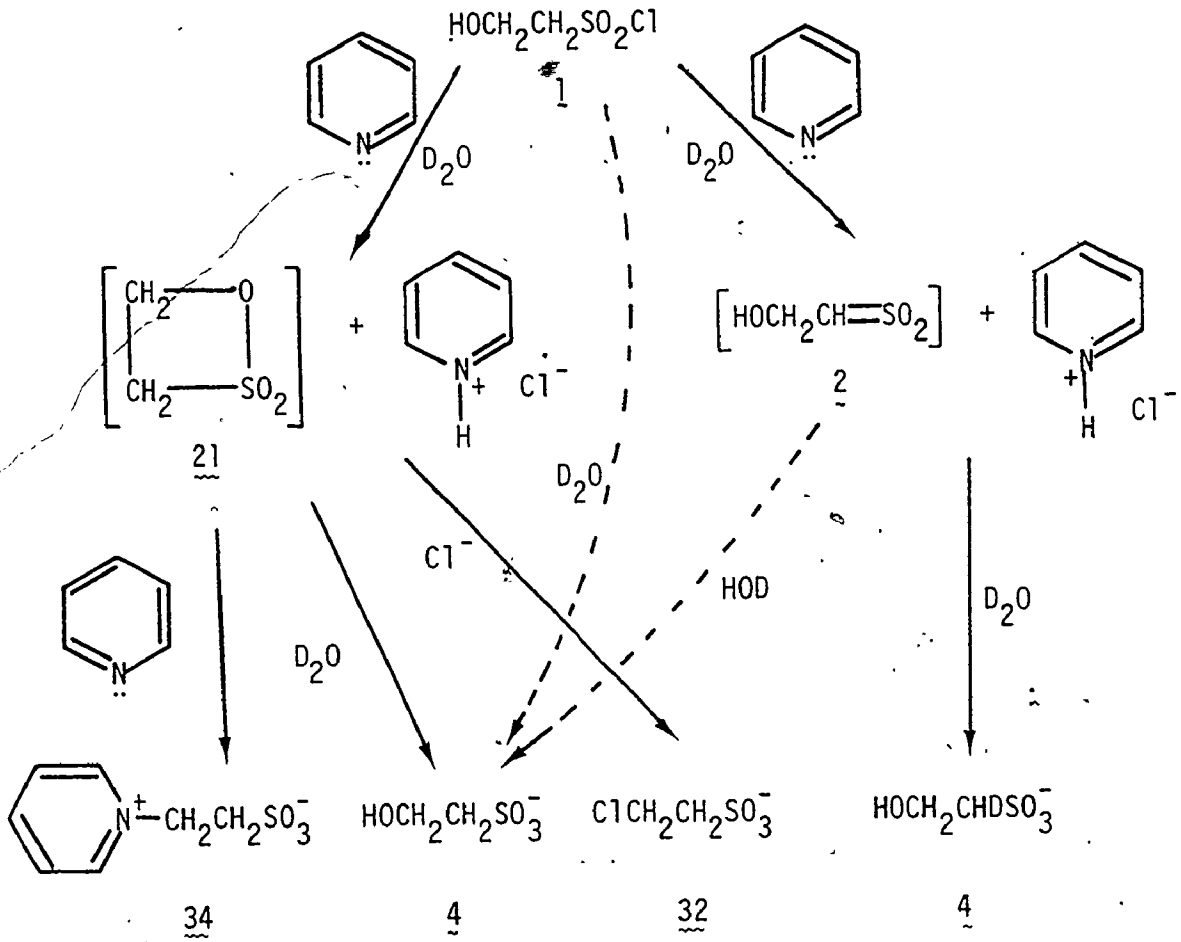
*It is also possible that some undeuterated isethionate (4) may be derived by a general base catalysed hydrolysis reaction at the sulfonyl group of 1.

SCHEME 4.10


HOCH2CH2SO2Cl
1
D2O
D2O
[CH2—O / CH2—SO2]
21
+
N+ H Cl−
[HOCH2CH=SO2]
2
+
N+ H Cl−
D2O
Cl−
HOD
D2O
D2O
N±—CH2CH2SO3−
34
HOCH2CH2SO3−
4
ClCH2CH2SO3−
32
HOCH2CHDSO3−
4

at pH 4.0, it is presumably not an intermediate under the reaction conditions (0.1 M KCl) for the kinetic measurements performed with 3 in Chapter 1.

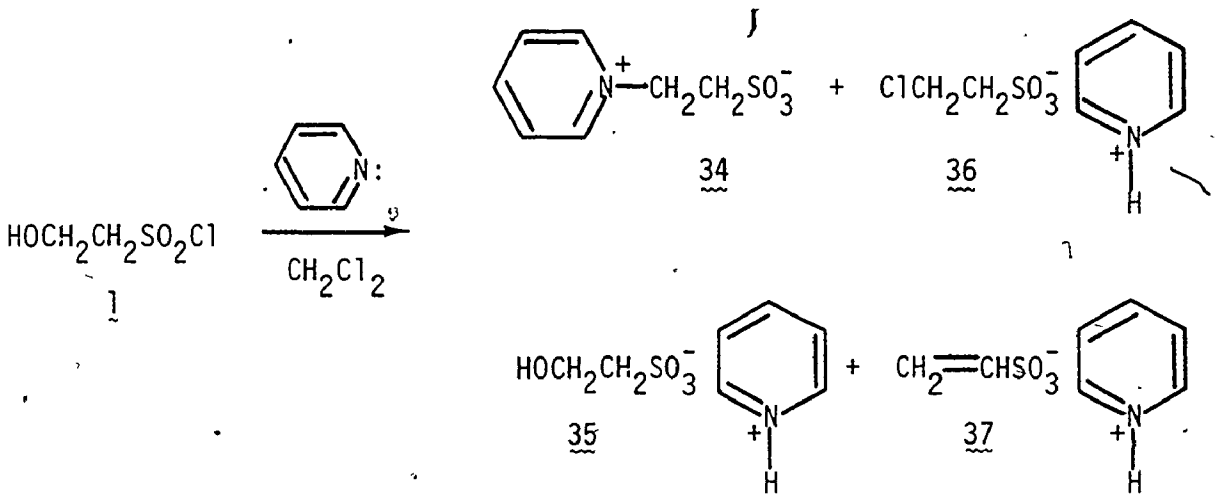
The intervention of 2-hydroxymethylsulfene (2) intermediate in the hydrolysis reactions of ethenesulfonyl chloride (3) is limited largely to the generation of isethionate anion (4), since little of 33 is generated from 2 (according to the results of the reaction of 2-hydroxyethanesulfonyl chloride (1) with pyridine in D_2O).

(iii) Reaction of 2-Hydroxyethanesulfonyl Chloride (1) with Pyridine in Methylene Chloride

2-Hydroxyethanesulfonyl chloride (1) was treated with an excess of pyridine in methylene chloride for one hour at room temperature. A few minutes after injection of pyridine into the methylene chloride solution of 1, a colorless precipitate was observed. After one hour the precipitate was filtered and established (by comparison with the ^1H n.m.r. spectrum of an authentic specimen) to be N-pyridinium ethanesulfonate (pyridine betaine) (34). The solvent was evaporated, and the ^1H n.m.r. spectrum (D_2O) of the oily residue indicated the presence of pyridinium 2-chloroethanesulfonate (36) and pyridinium ethenesulfonate (37), with a trace of pyridinium isethionate (35) (all products were identified by comparison with spectra of authentic specimens. The reaction is shown in Scheme 4.11.

In a separate experiment, the reaction products 35, 36 and 37 were isolated as their corresponding sulfonic acids by the use of Rexyn 101 (H^+), a strong acid ion exchange resin. The acids were identified by comparison with ^1H n.m.r. spectra of authentic materials prepared by

SCHEME 4.11

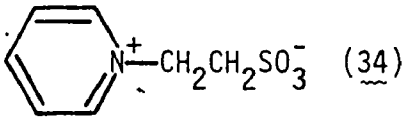
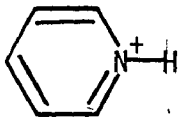
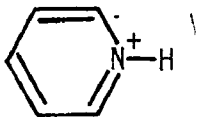
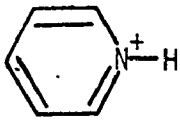


independent routes. The yields of these reaction products are given in Table 4.3 for both experiments. A control experiment performed with 35, 36, and 37 showed that these products were stable under the reaction conditions. Again the pyridine betaine (34) and pyridinium 2-chloroethanesulfonate (36) products are most likely derived from an intermediate β-sultone (21), but the extent of hydroxymethylsulfene (2) formation in this reaction is uncertain. Pyridinium isethionate (35) may have been generated either from the sultone (21), from the sulfene (2) or by direct attack upon 1 by any adventitious water present in the medium.

To establish whether the sulfene (2) is generated from reactions of the hydroxysulfonyl chloride (1) with tertiary amines in an organic medium, the reactions of 1 with tertiary amines in the presence of a primary alcohol (including a deuterated sulfene trapping agent, 1-butanol-O-d) in methylene chloride were investigated. The results of these reactions are presented in the next section.

TABLE 4.3

Reaction of 2-Hydroxyethanesulfonyl Chloride (1) with Pyridine in Methylene Chloride

Product	Yield (%)
 (34)	$50^{(a)}$, $61^{(a)}$
$ClCH_2CH_2SO_3^-$  (36)	$34^{(b)}$, $25^{(b,c)}$
$CH_2{=}CHSO_3^-$  (37)	$10^{(b)}$, $13^{(b,c)}$
$HOCH_2CH_2SO_3^-$  (35)	$1^{(b)}$, $1^{(b,c)}$

a) isolated yield.

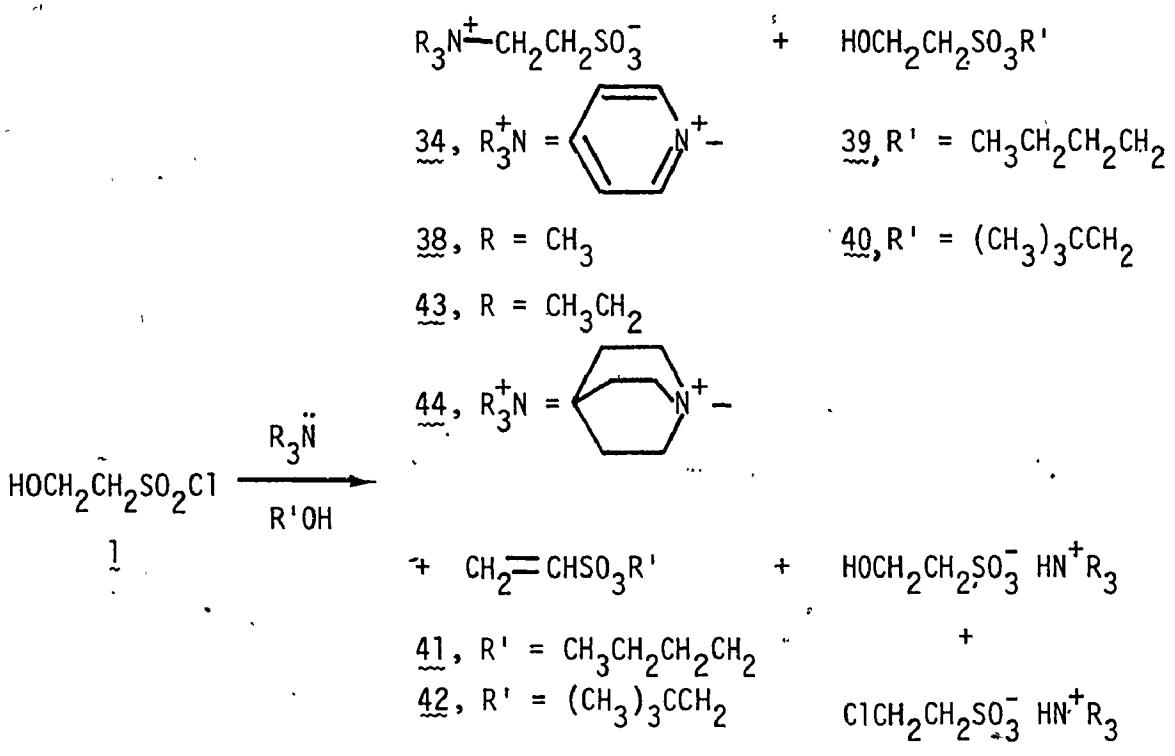
b) Yields were estimated by integration of the ^1H n.m.r. spectrum of the mixture of products taken with the weight of the mixture.

c) These yields refer to the reaction where 35, 36, 37 were converted to their corresponding sulfonic acids by use of Rexyn 101 (H^+).

(iv) Reactions of 2-Hydroxyethanesulfonyl Chloride (1) with Tertiary Amines and Primary Alcohols in Methylene Chloride

The sulfonyl chloride (1) was treated with a series of tertiary amines in methylene chloride solution containing either 1-butanol or neopentyl alcohol (usually in large excess) at room temperature. The reaction products were identified by comparison with ^1H n.m.r. spectra of authentic specimens. The reaction products are shown below in Scheme 4.12.

SCHEME 4.12



The sulfonate salts were isolated as their corresponding sulfonic acids, 2-hydroxyethanesulfonic (isethionic acid) and 2-chloroethanesulfonic acid. Control experiments performed with authentic samples of 34,

trimethyl betaine (39), isethionate anion (4) and 2-chloroethanesulfonate anion (32) demonstrated that these products were stable under the conditions of the workup procedure. The relative proportions of the products are given in Table 4.4.

Since it had been well established (34) that sulfonate esters of primary alcohols were readily dealkylated in the presence of a tertiary amine, it was probable that some of the isolated isethionic acid in these reactions was generated from a dealkylation reaction of the 2-hydroxyethanesulfonate ester. The rates of these reactions would be expected to be dependent upon the nucleophilicity of the amine along with the type of sulfonate ester present, among other factors.

A slow reaction of 39 and 41 with pyridine was observed when these esters were isolated in the presence of pyridine. The alkylation of pyridine occurred over several hours, but the sulfonate esters (39), (41) could not be isolated free of their dealkylation products. For this reason subsequent experiments employed neopentyl alcohol when unhindered bases were used.

When triethylamine was used as the tertiary amine base, the dealkylation reaction of 39 and 41 with this base appeared to be a very slow reaction, as judged by the negligible amount of isethionic acid formed in this reaction. This effect was probably due to the greater steric bulk of triethylamine relative to trimethylamine and pyridine.

Treatment of butyl 2-hydroxyethanesulfonate (39) with a large excess of trimethylamine in the presence of 1-butanol resulted in the formation of some (16%) isethionate anion (4) and a trace amount (2%) of trimethyl betaine (38), with the remainder of the material being unreacted ester

TABLE 4.4

Reactions of 2-Hydroxyethanesulfenyl Chloride (1) with Tertiary Amines in the Presence of Primary Alcohols

Alcohol	Amine	# (equivalents) amine	pK_a[a]	Time (min.)	$R_3\overset{+}{N}CH_2CH_2SO_3^-$[d]	Relative Proportions of Products (%)[c] $CH_2=CHSO_3R'$	$HOCH_2CH_2SO_3R'$	$ClCH_2CH_2SO_3H$	$HOCH_2CH_2SO_3H$
1-butanol	$(CH_3)_3\ddot{N}$	(1.7)	9.80	60	38	3	33	20	7
1-butanol-O-d	$(CH_3)_3\ddot{N}$	(1.7)		60	40	3	40[e]	14	3
neopentyl alcohol	$(CH_3)_3\ddot{N}$	(1.7)		60	51	6	25	5	10
1-butanol	$(CH_3CH_2)_3\ddot{N}$	(10)	10.72	3	22	3	27	43	<1
1-butanol	pyridine	(10)	5.23	10	57	3[b]	7[b]	28	<1
neopentyl alcohol	pyridine	(1.6)		60	35	2	8	40	8
1-butanol	quinuclidine	(1.5)	10.65	60	29	<1	30	21	10

(a) from reference (37).

(b) estimated from yields of dealkylation products.

(c) The yields of esters and acids (isolated as mixtures) were determined by ^1H n.m.r. integration taken with the weight of the mixtures.

(d) isolated yield.

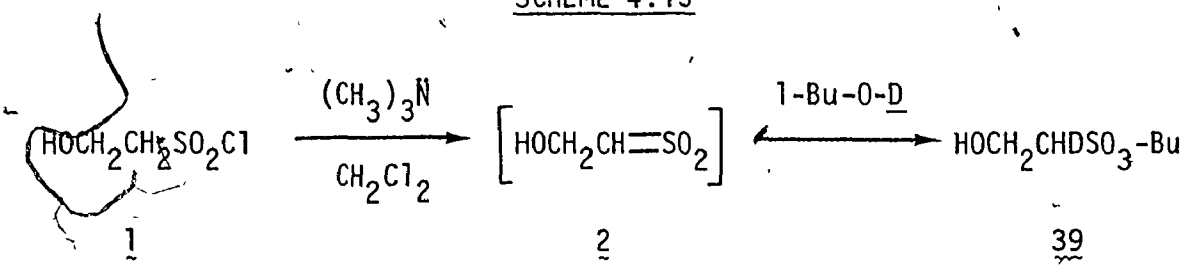
(e) monodeuterated ester

(39). The very low conversion of 39 to 38 in this reaction suggests that for the reaction of the sulfonyl chloride (1) with a slight excess of trimethylamine, the betaine (38) was probably generated by an alternative route, and not from the ester (39).

The reaction of the sulfonyl chloride (1) with 1-butanol-O-d and trimethylamine was also examined. The products were again identified by ^{1}H n.m.r. spectroscopy. No deuterium was observed to have been incorporated into either of the isolated β-substituted ethanesulfonic acids, butyl ethenesulfonate (41) or trimethyl betaine (38). However, butyl 2-hydroxyethanesulfonate (39) was estimated (by ^{1}H n.m.r. integration) to be ≥80% monodeuterated at the α carbon. The observed deuteration pattern in the products is consistent with the generation of the trimethyl betaine (38), 2-chloroethanesulfonate anion (32) and isethionate anion (4) from the intermediate β-sultone (21). The lack of deuterium in the sulfonic acid analogues of 4 and 32 suggests that the alkylation of trimethylamine by butyl 2-hydroxyethanesulfonate (39) did not occur under these conditions.

The observation of α monodeuterated ester (39) here is interpreted as evidence for the intermediacy of the hydroxymethylsulfene (2) in this reaction of the hydroxysulfonyl chloride (1), as shown in Scheme 4.13.

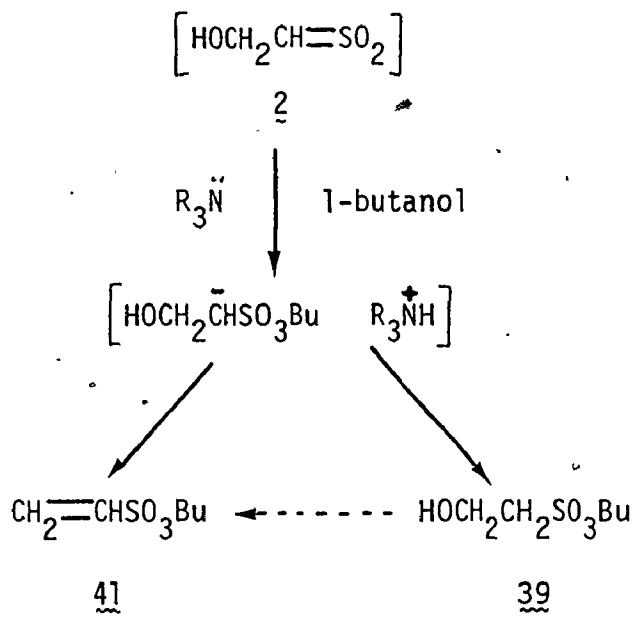
SCHEME 4.13



1 2 39

Butyl ethenesulfonate (42) may also have been generated from 2 if a carbanion intermediate is formed when an alcohol is added to the sulfene (2), as shown in Scheme 4.14. Elimination of hydroxide ion from the carbanion intermediate could yield 41, while protonation of this intermediate would furnish 39 as the major product of trapping the sulfene with 1-butanol.

SCHEME 4.14



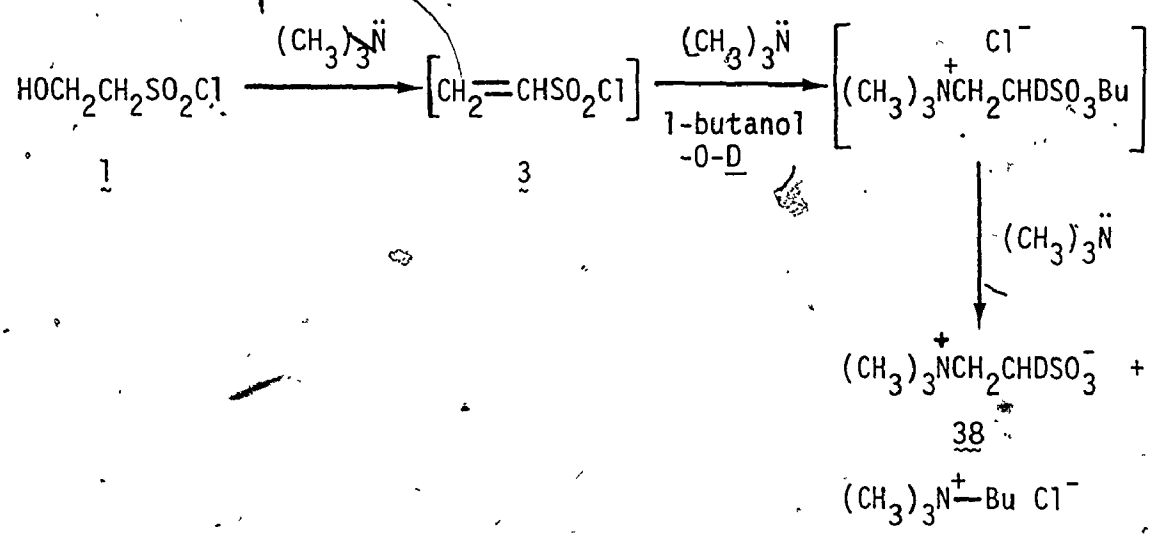
The isolation of completely undeuterated 41 in this reaction was evidence against the conversion of 39 to 41 under these conditions, since partly monodeuterated 41 would have been observed if this reaction had occurred to any large extent.

This result was confirmed by treating neopentyl 2-hydroxyethanesulfonate (40) with a solution of triethylamine, triethylammonium chloride, and neopentyl alcohol in methylene chloride for one hour at room temperature. After workup an 85% yield of unreacted 40 was

recovered, with no sign of any neopentyl ethenesulfonate (42) in the ^{1}H n.m.r. spectrum. The possibility that some 42 was formed from 40, followed by a fast reaction to produce a neopentyl [2] betylate was also investigated. The ester (42) was treated with a $CDCl_3$ solution of triethylamine, triethylammonium chloride and neopentyl alcohol. After 24 hours the ^{1}H n.m.r. spectrum of the solution showed no observable reaction. From these experiments it was concluded that the 2-hydroxyethanesulfonate esters were not the precursors of the ethenesulfonate esters, and the ethenesulfonate esters did not generate [2]-betylates under the conditions of the reactions of 1 with alcohols and tertiary amines.

The possibility that ethenesulfonyl chloride (3) was a reactive intermediate in the reaction of the hydroxysulfonyl chloride (1) with trimethylamine and a primary alcohol was reduced when the betaine (38) was isolated with no observed incorporation of deuterium. Based upon previous results for the reactions of 3 with tertiary amines in D_2O (see Chapter 1) or alcohols in CH_2Cl_2 (see Chapter 2 and (35)), both of which have been shown to proceed by vinylogous nucleophilic attack, the reaction of 3 with trimethylamine and 1-butanol-O-d would generate significant amounts of α monodeuterated betaine (38), as shown in Scheme 4.15. This was not the observed result. Ethenesulfonyl chloride (3) is most probably not a reactive intermediate in the reactions of 1 with other tertiary amines, either.

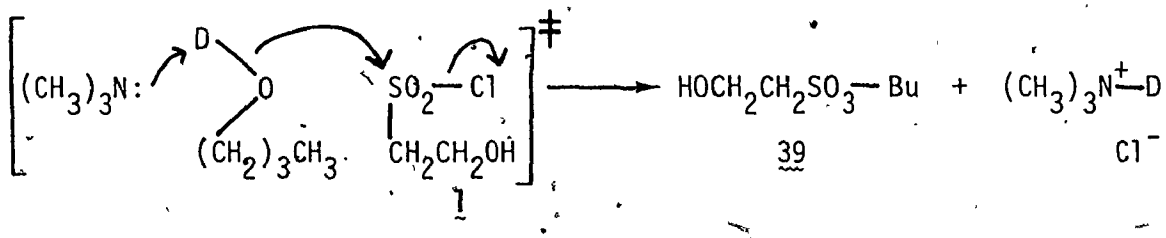
SCHEME 4.15



Changing the alcohol from 1-butanol to neopentyl alcohol in the reactions of 1 with triethylamine in methylene chloride resulted in an altered ratio of the 2-hydroxyethanesulfonate ester to ethenesulfonate ester (12:1 with 1-butanol versus 4:1 with neopentyl alcohol). There may be several reasons for these results. One possible explanation is that some of the additional butyl 2-hydroxyethanesulfonate (39) (derived from the reaction of 1 with 1-butanol) could be produced by a termolecular general base catalysed alcoholysis reaction of 1, as shown in Scheme 4.16. This process could conceivably be an easier reaction with the less bulky 1-butanol than with neopentyl alcohol.

If true, this could help to explain the observation of some undeuterated 39 in the reaction of 1 with trimethylamine and 1-butanol-O-d.

SCHEME 4.16



In this context it should be remembered that the relative importance of the termolecular general base catalysed alcoholysis reactions of alkanesulfonyl chlorides has not yet been established.

Comparing the relative proportions of the products given in Table 4.2, it is evident that the total of 2-chloroethanesulfonate anion (32) and the amine betaine (34,43) was significantly larger when pyridine was employed in place of triethylamine (with other variables held constant).

These results are consistent with the generation of proportionately larger amounts of the β-sultone (21) with the weaker amine base (pK_a of pyridine: 5.23, versus 10.72 for triethylamine). The consequence of a larger proportion of the sulfonyl chloride (1) being converted to 21 is a decreased amount of the sulfene (2) generated in these reactions. The apparent decrease in the extent of sulfene formation with decreasing tertiary amine strength has some recent precedent (36) in the reactions of a few alkanesulfonyl chlorides with tertiary amines in the presence of primary alcohols. In the present reaction, it is apparent that there may be a competition between the relative rates of formation of the sulfene (2) and the β-sultone (21), and the relative ease of formation of these intermediates may well be dependent upon a variety of factors.

The reaction of 2-hydroxyethanesulfonyl chloride (1) with tertiary amines and primary alcohols to generate 2-hydroxyethanesulfonate esters represents a method for the preparation of these esters, albeit in modest yields to date.* Prior to this work the only other report of the

*Recently, a general method for making hydroxyalkanesulfonate esters has been developed in this laboratory (42).

synthesis of a 2-hydroxyethanesulfonate ester was the preparation of ethyl 2-hydroxyethanesulfonate (45) from a reaction of silver 2-hydroxyethanesulfonate (46) with ethyl iodide (39). A monograph (40) has described the yield of the ester (45) obtained from this reaction as "minute".

$$\underset{\underline{46}}{HOCH_2CH_2SO_3^- Ag^+} \xrightarrow{CH_3CH_2I} \underset{\underline{45}}{HOCH_2CH_2SO_3CH_2CH_3} + AgI$$

For comparison, when 2-chloroethanesulfonyl chloride (5) was treated with tertiary amines in the presence of primary alcohols (41), the only observed products were the ethenesulfonate ester and the [2] betylate. No 2-chloroethanesulfonate esters were observed (see also Chapter 3).

$$\underset{\underline{5}}{ClCH_2CH_2SO_2Cl} \xrightarrow[R'OH]{R_3\ddot{N}} \underset{Cl^-}{R_3\overset{+}{N}CH_2CH_2SO_3R'} + CH_2{=}CHSO_3R'$$

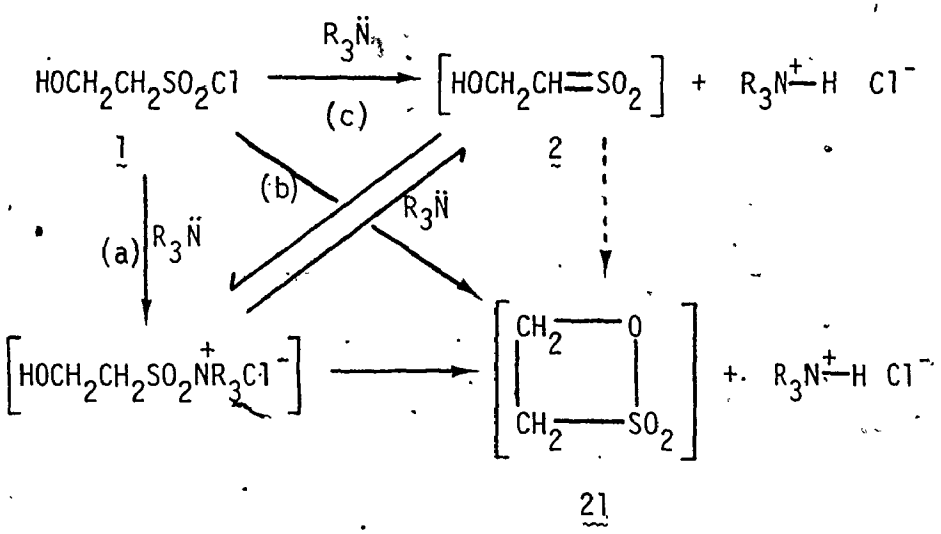
In the reactions of 2-hydroxyethanesulfonyl chloride (1) with tertiary amines, two reactive intermediates have been proposed to account for the formation of the observed reaction products. To date there is unambiguous evidence for the intermediacy of variously substituted sulfenes in several reactions (37). While the hydroxymethylsulfene (2) has not specifically been previously proposed, the β-hydroxymethyl substituent may not destabilize the parent sulfene structure ($CH_2{=}SO_2$) by an appreciable amount according to the theoretical calculations of Snyder (38). Therefore the existence of the sulfene (2) as an intermediate in some reactions of 1 would appear to be a

reasonable result.

As discussed earlier sultones of various ring sizes are well known, and β-sultones bearing electron withdrawing substituents have been isolated. Therefore, the proposed intermediacy of the unsubstituted β-sultone (21) in some reactions of 1 is also chemically reasonable.

The mechanism by which the proposed β-sultone (21) is generated from the hydroxysulfonyl chloride (1) in these reactions deserves some comment. There are three possible mechanisms by which 1 may be converted to 21 by a tertiary amine base, and these are shown in Scheme 4.17.

SCHEME 4.17



21

Mechanism (a) involves the generation of a sulfonylammonium ion intermediate from 1, followed by ring closure to give the β-sultone (21). Mechanism (b) is the concerted general base promoted cyclization of 1 to give 21. Mechanism (c) involves generation of the hydroxymethyl sulfene (2), followed by generation the sulfonylammonium ion and

then the sultone (21).*

The mechanisms involving the generation of an intermediate sulfonylammonium ion may be feasible only if collapse of this species to the β-sultone (21) was much faster than incorporation of deuterium into the sulfonylammonium ion in the presence of an unhindered tertiary amine and a deuterated sulfene trap. In this context, trialkyl(methylsulfonyl)ammonium ions have been shown to readily incorporate deuterium in the presence of a tertiary amine and either D_2O or a deuterated alcohol (44).

The evidence therefore is consistent with the base promoted intramolecular cyclization mechanism for the formation of the sultone (21) from the hydroxysulfonyl chloride (1) in these reactions (mechanism b, Scheme 4.17).

*A fourth mechanism involving a 4-Endo-Trigonal addition of 2 to generate the sultone 21 is not a likely possibility since these types of reactions are unknown, and are considered to be disfavored reactions at least for first row elements (43).

4.3 Conclusions

The aqueous chlorination of 2-mercaptoethanol (20) has resulted in the generation of 2-hydroxyethanesulfonyl chloride (1) in modest yields. This sulfonyl chloride bears two functional groups capable of mutual reaction. While the aqueous chlorination of 3-hydroxypropanethiol (28) did not generate any 3-hydroxypropanesulfonyl chloride (31), longer chain ω-hydroxyalkanethiols could become useful precursors to other ω-hydroxyalkanesulfonyl chlorides using this method. The solvolysis reactions of 1 in water and D_2O apparently results in the formation of appreciable quantities of an unsubstituted β-sultone (21) intermediate, as well as the conventional nucleophilic displacement reaction at sulfonyl sulfur by the solvent.

The reaction of 1 with pyridine in both D_2O and methylene chloride appears consistent with the generation of both the β-sultone (21) and the sulfene (2) intermediates as interpreted by the nature of the reaction products and their deuteration patterns. The reactions of 1 with primary alcohols in methylene chloride containing a tertiary amine resulted in modest yields of 2-hydroxyethanesulfonate esters. For the reactions of 1 in methylene chloride there appears to be a slight dependence upon the extent of sulfene (2) formation with the basicity of the tertiary amine employed, with stronger bases producing more sulfene (2) relative to sultone (21).

The most likely means of generating the β-sultone (21) from the sulfonyl chloride (1) with a tertiary amine is concluded to be the general base promoted 4-Exo-Tet cyclization reaction (mechanism (b) in Scheme 4.17).

4.4 Experimental

The general remarks given in the experimental section of Chapter 1 apply here as well. Anhydrous ether (Fisher) was used without further purification. Rexyn 101 (H^+) (Fisher) was used as supplied, usually in excess. 1,3-Propanedithiol, 1,3-propanesultone and 3-mercaptopropionic acid were obtained from the Aldrich Chemical Company, and were used as supplied.

An authentic specimen of butyl ethenesulfonate (41) was provided by Dr. M. Aslam (45). An authentic specimen of N-pyridinium 2-ethanesulfonate (pyridine betaine) (34) was prepared by the method of Le Berre et al (1). Neopentyl ethenesulfonate (42) was prepared by the method of King and Aslam (21) from 2-chloroethanesulfonyl chloride (5). The crude product obtained in this manner was distilled (b.p. 62°, 0.02 mm Hg) to afford the pure compound; ^{1}H n.m.r. ($CDCl_3$) δ: 0.98 (S, 9H), 3.77 (S, 2H), 6.1 - 6.7 (ABC multiplet, 3H).

A sample of 3-chloropropanesulfonyl chloride (28) was provided by J.D. Lock, who prepared it according to the method of Bliss et al (49).

Sodium 2-chloroethanesulfonate (32) (Aldrich) was recrystallized from absolute alcohol; ^{1}H n.m.r. (D_2O) δ: 3.38 (t, 2H), 3.90 (t, 2H). Sodium 2-hydroxyethanesulfonate (sodium isethionate) (4) (Eastman) was used without further purification; ^{1}H n.m.r. (D_2O) δ: 3.12 (t, 2H), 3.90 (t, 2H). Ethenesulfonic acid was provided by Dr. M. Aslam, who prepared it by hydrolysis of methyl ethenesulfonate; ^{1}H n.m.r. (T-60, D_2O) δ: 5.4 - 5.9 (m, 2H), 6.40 (d of d, 1H).

Pyridinium chloride, trimethylammonium chloride, and triethylammonium chloride were prepared by bubbling anhydrous HCl gas (Linde)

through a solution of the amine base in anhydrous benzene, followed by evaporation of the benzene. These amine hydrochlorides were used without further purification, but were stored in a desiccator over calcium chloride or phosphorus pentoxide (Fisher).

Preparation of 2-Hydroxyethanesulfonyl Chloride (1)

2-Mercaptoethanol (20) (Aldrich) (30 mL, 4.28×10^{-1} mol) was dissolved in water (100 mL) and cooled in an ice bath (initial temperature approximately 4°). Chlorine (Linde, Union Carbide Ltd.) was bubbled very rapidly into this solution over a period of 10 minutes with vigorous magnetic stirring. The now warm solution (temperature ~40°) was transferred to a separating funnel and extracted with benzene (4 × 50 mL) and the extracts combined. The aqueous solution was then extracted with methylene chloride (5 × 50 mL) and these extracts combined. After drying and filtration, the benzene extracts were evaporated to give an oil (11.3 g). The ^{1}H n.m.r. spectrum ($CDCl_3$) of this material showed a large singlet at δ: 4.0 ppm with surrounding multiplets from 3.5 - 4.5 ppm, and was consistent with a mixture of 2-chloroethanesulfonyl chloride (5) and 2-hydroxyethanesulfonyl chloride (1), in relative proportions 57% and 43%, respectively (as judged by integration of these absorptions). After drying, filtration and evaporation of the methylene chloride extracts, a pale yellow viscous oil was obtained (8.8 g). The ^{1}H n.m.r. spectrum ($CDCl_3$) of this material showed only the multiplets at ~4.0 ppm present, indicating the absence of 5. The original aqueous solution was then saturated with sodium chloride, and extracted with more methylene chloride (4 × 50 mL),

then continuously extracted with methylene chloride for 3 hours. Drying, filtering and evaporation of these extracts gave a further 8.4 g of a colorless viscous oil; (overall yield of 1 ~30%, yield of 5 ~10%); ^{1}H n.m.r. ($CDCl_3$) of the pure sulfonyl chloride (1) δ: 2.82 (s, 1H), 3.98 (m, 2H), 4.28 (m, 2H) (see Figure 4.1); ^{13}C n.m.r. ($CDCl_3$) δ: 56.9, 67.6; i.r. (CH_2Cl_2) 3590 (s), 3460 (b,w), 3060 (w), 2925 (w), 2890 (w), 1375 (vs), 1168 (vs), 1058 (vs), 1015 (m), 840 (w), 592 (s), 550 (b,s) cm^{-1}. Anal. calcd. for $C_2H_5ClO_3S$: C, 16.61; H, 3.49; S, 22.18; Cl, 24.52. Found: C, 16.88; H, 3.63; S, 22.23; Cl, 24,30; n_D^{25} 1.4902.

A reasonably pure specimen of 1 could also be obtained by extraction of the aqueous solution only with methylene chloride. The crude mixture of sulfonyl chlorides isolated in this manner was then triturated with cyclohexane repeatedly to remove 2-chloroethanesulfonyl chloride (5), leaving 2-hydroxyethanesulfonyl chloride (1) behind as a colorless viscous oil.

/The rate of addition of chlorine in this preparation was found to be very important in obtaining a good yield of 1. If the rate of addition was not fast or if the period of chlorination was less than 10 minutes, then the isolated material had the odour of reduced sulfur compounds and the ^{1}H n.m.r. spectrum showed extra absorptions in the regions δ: 2.6 - 3.0, 3.5 - 3.9 ppm. The addition of ice during the chlorination period (final temperature ~30°) or the choice of methylene chloride instead of benzene for the initial extractions had little effect on the overall yield of 1 obtained.

In a control experiment, 1.50 g of the sulfonyl chloride (1) was dissolved in a saturated solution of sodium chloride in water (50 mL) at room temperature. After standing for 2 - 3 minutes, the solution

was extracted with methylene chloride (3 × 50 mL). The organic extracts were combined, dried, filtered and evaporated to yield 1.32 g (85%) of the sulfonyl chloride (1).

Stability of 2-Hydroxyethanesulfonyl Chloride (1)

(a) In chloroform solution

The sulfonyl chloride (1) (0.006 g, 4.1×10^{-5} mol) was dissolved in $CDCl_3$ (0.5 mL) and placed in an n.m.r. tube (wrapped in aluminum foil) at room temperature. ^1H n.m.r. spectra of this solution were taken at regular intervals, and the sample showed no apparent decomposition after 8 months at room temperature.

(b) In the absence of solvent

A neat sample of the sulfonyl chloride (1) (0.275 g, 1.9×10^{-3} mol) was allowed to stand at room temperature while wrapped with aluminum foil. At regular intervals a portion of the sample was removed and analysed by ^1H n.m.r. spectroscopy. After 3 weeks approximately half of the sample was judged to have decomposed (general broadening of the absorptions attributed to 1 in the ^1H n.m.r. spectrum taken with new absorptions in the region δ: 3.4 - 5.0 ppm). The exact nature of these decomposition products was not determined, but 2-chloroethanesulfonyl chloride (5) and ethenesulfonyl chloride (1) were not observed.

Reaction of 2-Hydroxyethanesulfonyl Chloride (1) with Acetyl Chloride

2-Hydroxyethanesulfonyl chloride (1) (1.5 g, 1.0×10^{-2} mol) was combined with acetyl chloride (Fisher) (5.0 mL, 7.0×10^{-2} mol) at room temperature. Upon mixing gas evolution was observed. After 72 hours at room temperature the excess acetyl chloride was evaporated, and the oily residue was distilled under reduced pressure (2.5 mm Hg) in a cold finger apparatus to yield a clear colorless oil (1.6 g, 83%). The refractive index, i.r. and ^{1}H n.m.r. spectra of this material were identical to those of an authentic specimen of 2-acetoxyethanesulfonyl chloride (22), prepared by the method described below.

Preparation of 2-Acetoxyethanesulfonyl Chloride (22)

2-Acetoxyethanesulfonyl chloride (22) was prepared by the method of Anschütz (19) from sodium 2-acetoxyethanesulfonate (46) and phosphorus pentachloride (Fisher). The pure compound was obtained by distillation of the crude product under reduced pressure (b.p. 72 - 73°, 0.1 mm Hg); ^{1}H n.m.r. ($CDCl_3$) δ: 2.13 (s, 3H), 4.07 (t, 2H), 4.65 (t, 2H); i.r. (neat) 2995 (w), 2935 (w), 1745 (vs), 1370 (vs), 1230 (vs), 1160 (vs), 1070 (s), 1035 (s), 705 (s), 535 (s) cm^{-1}; n_D^{25} 1.4639, lit. (19) n_D^{25} 1.4633.

Chlorination of 2-Mercaptoethanol (20) in Aqueous Acetic Acid

2-Mercaptoethanol (20) (20 mL, 2.85×10^{-1} mol) was dissolved in a 1:1 mixture (100 mL) of water and acetic acid, and the solution cooled in an ice bath. Chlorine was bubbled into this solution with vigorous magnetic stirring for 30 minutes. The yellow solution was extracted

with methylene chloride (4 × 30 mL), the extracts were combined, dried, filtered and the solvent evaporated to give a colorless oil which had a strong odour of acetic acid. This was removed by azeotroping with toluene. The residue (37 g) was then distilled under reduced pressure (b.p. 70 - 72°, 0.1 mm Hg) to yield a colorless oil (15 g, 30%) whose ^{1}H n.m.r., i.r. spectra were identical with those of an authentic specimen of 2-acetoxyethanesulfonyl chloride (22).

Preparation of 2-Hydroxyethanesulfinic Acid (23)

A solution of sodium sulfite (Fisher) (10 g, 7.93×10^{-2} mol) in water (50 mL) was prepared. An aliquot (15 mL) of this solution was added to 2-hydroxyethanesulfonyl chloride (1) (1.0 g, 6.9×10^{-2} mol) at room temperature. The resulting solution was allowed to stand at room temperature for 2 hours, then extracted twice with methylene chloride. The pH of the aqueous layer was adjusted to 1.0 with 2 M sulfuric acid, and then continuously extracted with ether for 72 hours. The organic extract was dried, filtered and evaporated to yield a light yellow oil (0.55 g, 75%), n_D^{25} 1.4235; ^{1}H n.m.r. (D_2O) δ: 3.04 (t, 2H), 4.01 (t, 2H); i.r. (neat) 3360 (b), 1058 (s), 813 (m) cm^{-1}.

Apparent pK_a Determination of 2-Hydroxyethanesulfinic Acid (23) in Water at 25.0°C

The pH titration curve for 2-hydroxyethanesulfinic acid (23) was determined using the pH-stat apparatus previously described (Chapter 1). The apparent pK_a was determined from the equivalence point in the titration curve for this acid. The data for this curve appears below.

TABLE 4.5 Titration Curve Data for 2-Hydroxyethanesulfinic Acid

H_2O: 50 mL Titrant: 1.0 M sodium hydroxide

pH	Titre (mL)
2.45	0
2.47	0.0502
2.55	0.1000
2.69	0.1700
2.80	0.2000
2.98	0.2500
3.30	0.2900
3.98	0.3200
5.51	0.3300
9.60	0.3410
10.10	0.3500
10.40	0.3600
10.69	0.3800
10.87	0.4000
10.99	0.4200
11.12	0.4500

equivalence point: 0.335 mL apparent pK_a: 2.68 (uncorrected)

Chlorination of 2-Hydroxyethanesulfinic Acid (23) in Deuterium Oxide

2-Hydroxyethanesulfinic acid (23) (0.050 g, 4.5×10^{-4} mol) was dissolved in D_2O (0.5 mL) and placed in an n.m.r. tube. Chlorine was bubbled into this solution for 10 minutes at room temperature. After this time the ^1H n.m.r. spectrum indicated the presence of 2-hydroxyethanesulfonyl chloride (1), with a trace amount (~5%) of isethionic acid.

Preparation of Sodium 2-Hydroxyethanesulfinate (24)

2-Hydroxyethanesulfinic acid (23) (0.750 g, 6.82×10^{-3} mol) was dissolved in water (10 mL) and the pH adjusted to 6.0 with 1.0 M sodium hydroxide solution. After standing for 10 minutes at room temperature the solvent was evaporated to yield a gummy residue which crystallized upon standing under reduced pressure (0.83 g, 92%), m.p. 81 - 83°; ^{1}H n.m.r. (D_2O) δ: 2.58 (t, 2H), 3.91 (t, 2H). The salt (24) was used without further purification in the following reaction.

Reaction of Sodium 2-Hydroxyethanesulfinate (24) with Ethyl Iodide

The sodium sulfinate (24) (0.75 g, 5.68×10^{-3} mol) was dissolved in absolute alcohol (25 mL) containing ethyl iodide (Fisher) (9.75 g, 6.25×10^{-2} mol). The solution was refluxed for 22 hours, then evaporated under reduced pressure to yield a red solid. This residue was triturated with chloroform (3 × 25 mL), the extracts combined, dried and the solvent removed to yield a red oil (0.45 g, 58%). The oil was dissolved in water (10 mL) and maintained at pH 10 - 11 with 1.0 M NaOH solution for 2 hours. Extraction with chloroform gave, after drying, filtering and removal of the solvent a light yellow oil (0.100 g, 15%). Crystallization and recrystallization of this material from benzene gave colorless needles (0.017 g) whose m.p. and ^{1}H n.m.r., i.r. spectra were identical to those of an authentic sample of ethyl 2-hydroxyethylsulfone (25) prepared as described below.

Preparation of Ethyl 2-Hydroxyethylsulfone (25)

Utilizing a slight modification of the literature (47) procedure, freshly recrystallized sodium ethanesulfinate (3.0 g, 2.59×10^{-2} mol) was dissolved in a mixture of ethanol (30 mL) and water (20 mL). To this solution 2-chloroethanol (BDH) (2.1 g, 2.62×10^{-2} mol) was added and the solution heated on a steam bath for 50 hours. Evaporation of the solvent under reduced pressure gave a colorless solid which was dissolved in water and continuously extracted with chloroform for 72 hours. The organic layer was dried, filtered and the solvent evaporated to yield a yellow oil (1.0 g). Colorless needles (0.175 g, 5%) were obtained from benzene, m.p. 40.5 - 42°; ^{1}H n.m.r. ($CDCl_3$) δ: 1.42 (t, 3H), 2.36 (s, 1H), 3.00 - 3.29 (m, 4H), 4.14 (m, 2H); i.r. ($CHCl_3$) 3350 (b,w), 3028 (m), 2945 (w), 2892 (w), 1460 (w), 1410 (w), 1315 (vs), 1280 (w), 1235 (w), 1128 (vs), 1063 (m) cm^{-1}.

Preparation of Sodium Ethanesulfinate

Ethanesulfonyl chloride (Eastman) (10 g, 7.8×10^{-2} mol) was combined with a solution of sodium sulfite (20 g, 1.6×10^{-1} mol) in water (100 mL) at room temperature. After standing for one hour the solution was cooled in an ice bath, and the pH adjusted to 1.0 with concentrated sulfuric acid solution. The aqueous solution was then continuously extracted with ether for 48 hours. The ether extract was dried, filtered and evaporated to yield a pale yellow oil (7.0 g, 96%). A sample (5.0 g) of this oil was dissolved in water (10 mL) and the pH adjusted to 7.0 with 1.0 M sodium hydroxide solution. The solvent was evaporated to yield a colorless solid which was recrystallized from 95% alcohol

(yield 3.0 g, 33%), decomp. >200°; ^{1}H n.m.r. (D_2O) δ: 1.09 (t, 3H), 2.35 (q, 2H); i.r. (nujol) 1185 (b,w), 1040 (s), 1010 (s), 979 (s), 665 (s) cm^{-1}.

Preparation of Barium 2-Hydroxyethanesulfinate (13)

A mixture of barium hydroxide · 8 H_2O (Fisher) (0.387 g, 1.23×10^{-3} mol) in water (20 mL) was combined with 2-hydroxyethanesulfinic acid (23) (0.270 g, 2.45×10^{-3} mol) at room temperature. After stirring for 75 minutes, the solvent was evaporated under reduced pressure (using water bath-temperature ≤35°) to yield an off-white solid (0.430 g, 50%), which decomposed >350°; ^{1}H n.m.r. (D_2O) δ: 2.60 (t, 2H), 3.92 (t, 2H); i.r. (nujol) 1060 (m), 1010 (sh), 985 (s), 950 (m) cm^{-1}. Anal. calcd. for $BaC_4H_{10}O_6S_2$: C, 13.51; H, 2.83. Found: C, 13.22; H, 3.09.

Aqueous Chlorination of 3-Mercaptopropanol (27)

3-Mercaptopropanol (27) (1.3 g, 1.4×10^{-2} mol, prepared according to the method of Djerassi and Gorman (48) from 3-mercaptopropionic acid) was dissolved in water (50 mL) and cooled in an ice bath. Chlorine was bubbled into this solution with magnetic stirring for 10 minutes. The solution was extracted several times with methylene chloride, the extracts were combined, dried, filtered and the solvent evaporated to yield a colorless oil (1.0 g). The ^{1}H n.m.r. spectrum ($CDCl_3$) of this material indicated a 1:1 mixture of 1,3-propanesultone (29) and 3-chloropropanesulfonyl chloride (28), each in 24% yield.

Aqueous Chlorination of 1,3-Propanesultine (31)

1,3-Propanesultine (31) (0.45 g, 4.24×10^{-3} mol, prepared according to the method of Harpp (32) from 1,3-propanedithiol) was dissolved in water (50 mL) and cooled in an ice bath. Chlorine was bubbled into this solution with magnetic stirring for 10 minutes. The solution was then extracted with methylene chloride (4 × 30 mL). The organic extracts were combined, dried, filtered and the solvent evaporated to yield a colorless oil (0.50 g). The ^{1}H n.m.r. spectrum ($CDCl_3$) of this material indicated a 6:1 ratio of 1,3-propanesultone (29) (77%) and 3-chloropropanesulfonyl chloride (28) (13%).

Hydrolysis of 2-Hydroxyethanesulfonyl Chloride (1) at 25.0°C

(a) pH 4.0

The sulfonyl chloride (1) (0.147 g, 1.02×10^{-3} mol) was dissolved in dry 1,2-dimethoxyethane (DME) (1.0 mL). This solution was injected with stirring into water (50 mL) maintained at 25.0° and pH 4.0 using the pH-stat apparatus with 0.1 M sodium hydroxide titrant. After 90 minutes the pH was adjusted to 7.0 and the solvent evaporated to yield a colorless solid. The ^{1}H n.m.r. spectrum (D_2O) of this material showed absorptions only in the region δ: 2.9 - 4.0 ppm, corresponding to sodium isethionate (4), sodium 2-chloroethanesulfonate (32) and an unidentified material. The identity of the products were established by comparison with ^{1}H n.m.r. spectra of the authentic specimens. Integration of these peaks in the ^{1}H n.m.r. spectrum gave the relative proportions as 87%, 8%, 5%, respectively.

(b) pH 11.0

The sulfonyl chloride (1) (0.150 g, 1.03×10^{-2} mol) was dissolved in dry DME (1.0 mL) and the solution injected with stirring into water (50 mL) maintained at 25.0° and pH 11.0 with 0.1 M sodium hydroxide titrant. After 5 minutes the pH of the solution was adjusted to 7.0 with concentrated hydrochloric acid solution, and the solvent evaporated. The ^{1}H n.m.r. spectrum (D_2O) of the colorless residue obtained in this manner showed peaks mainly in the region δ: 2.5 - 4.0 ppm, indicating the presence of sodium isethionate (4), sodium 2-chloroethanesulfonate (32), and some unidentified material. The relative proportions of these products (determined by integration of the methylene peaks in this region) were 76%, 7%, 16%, respectively. A trace (~1%) of sodium ethenesulfonate (33) at δ: 5.5 - 7.0 ppm was also observed.

Hydrolysis of 2-Hydroxyethanesulfonyl Chloride (1) in Water Containing Potassium Chloride at 25.0°C

(a) pH 4.0, 0.1 M KCl

The sulfonyl chloride (1) (0.125 g, 8.62×10^{-4} mol) was dissolved in dry DME (1.0 mL) and injected into a stirred solution of potassium chloride (Fisher) (0.400 g, 5.36×10^{-3} mol) in water (50 mL) maintained at 25.0° and pH 4.0 with 1.0 M sodium hydroxide titrant. After stirring overnight the pH was adjusted to 7.0 and the solvent evaporated. The ^{1}H n.m.r. spectrum (D_2O) of the colorless residue showed absorptions at δ: 3.1 - 4.0 ppm only, indicating the presence of isethionate anion (4) and 2-chloroethanesulfonate anion (32). The relative proportions of these two products were determined (by integration of the methylene absorptions at δ: 3.12, 3.34 ppm) to be 80% and 20%, respectively.

(b) pH 4.0, 0.54 M KCl

The sulfonyl chloride (1) (0.154 g, 1.06×10^{-3} mol) was dissolved in DME (1.0 mL) and injected into a stirred solution of potassium chloride (2.0 g, 2.7×10^{-2} mol) in water (50 mL) maintained at 25.0° and pH 4.0. After 30 minutes the pH was adjusted to 7.0 with 1.0 M sodium hydroxide, and the solvent evaporated. The ^{1}H n.m.r. spectrum (D_2O) of the residue obtained in this manner showed absorptions at δ: 3.1 - 4.0 ppm, indicating the presence of sodium isethionate (4) and sodium 2-chloroethanesulfonate (32) in an equimolar ratio (as judged by ^{1}H n.m.r. integration of the absorptions at δ: 3.12 and 3.34 ppm).

(c) pH 11.0, 0.1 M KCl

The sulfonyl chloride (1) (0.100 g, 6.9×10^{-4} mol) was dissolved in dry DME (1.0 mL) and the solution injected into water (50 mL) containing potassium chloride (0.400 g, 5.36×10^{-3} mol) maintained at 25.0° and pH 11.0 with 1.0 M sodium hydroxide titrant. After 30 minutes the pH was adjusted to 7 with concentrated hydrochloric acid solution. Evaporation of the solvent gave a colorless residue whose ^{1}H n.m.r. spectrum (D_2O) exhibited absorptions in the region δ: 2.8 - 4.0 ppm, indicating the presence of isethionate anion (4), 2-chloroethanesulfonate anion (32), and some unidentified material, in relative proportions (determined by integration of the individual methylene absorptions in this region) of 79%, 20% and 1%, respectively.

Solvolysis of 2-Hydroxyethanesulfonyl Chloride (1) in Deuterium Oxide at 25.0°C

(a) Apparent pH 3.0

The sulfonyl chloride (1) (0.300 g, 2.07×10^{-3} mol) was dissolved in dry DME (1.0 mL), and the solution injected with stirring into D_2O (50 mL) at 25.0° and maintained at pH 3.0 with 3.9 M sodium deuteroxide titrant (prepared from sodium (0.90 g, 3.91×10^{-2} mol) and D_2O (10 mL)). After 30 minutes the solvent was evaporated to dryness. The ^1H n.m.r. spectrum (D_2O) of the colorless residue showed peaks in the region δ: 3.0 - 4.0 ppm, indicating the presence of sodium isethionate (4) and sodium 2-chloroethanesulfonate (32). No deuterium incorporation was observed in either of these products, as judged by the ^1H n.m.r. spectrum. The relative proportions of these two products were estimated to be 86% and 14%, respectively.

(b) Apparent pH 11.0

The sulfonyl chloride (1) (0.310 g, 2.14×10^{-2} mol) was dissolved in dry DME (1.0 mL) and this solution injected with stirring into D_2O (50 mL) maintained at 25.0° and apparent pH 11.0 with 3.9 M sodium deuteroxide titrant. After 10 minutes the pH was adjusted to 7.0 with 20% DCl/D_2O solution, and the solvent evaporated under reduced pressure. The ^1H n.m.r. spectrum (D_2O) of the colorless residue showed absorptions in the region δ: 2.5 - 4.0 ppm, indicating the presence of sodium isethionate (4) (90%), sodium 2-chloroethanesulfonate (32) (9%), and a trace amount (∿1%) of sodium ethenesulfonate (33) at δ: 5.5 - 7.0 ppm. No deuterium was observed in either 4 or 32, but a minute amount (∿10%) of 33 was estimated to have incorporated deuterium at the α vinyl position.

Control Experiment

Sodium 2-Chloroethanesulfonate (32) and Sodium Isethionate (4) in Water at 25.0°C

A solution of authentic samples of sodium isethionate (4) (0.100 g, 6.76×10^{-4} mol) and sodium 2-chloroethanesulfonate (32) (0.090 g, 5.39×10^{-4} mol) in water (100 mL) containing potassium chloride (0.800 g, 1.3×10^{-2} mol) was prepared for the experiments below.

(a) pH 4.0

An aliquot (50 mL) of this solution was adjusted to pH 4.0 with 1.0 M hydrochloric acid solution, and maintained at 25.0° for 2 hours. Evaporation of the solvent gave a colorless residue whose ^{1}H n.m.r. spectrum (D_2O) showed 4 and 32 in relative proportions 56% and 44% respectively (as judged by integration of the multiplets centered at δ3.12, 3.38 ppm), a relative ratio identical (within experimental error) to that of the original mixture.

(b) pH 10.5

The remainder of the original aqueous solution (50 mL) was adjusted to pH 10.5 with 0.1 M sodium hydroxide solution, and maintained at 25.0° for 35 minutes using the pH stat apparatus. The pH was then adjusted to 7 with 1.0 M hydrochloric acid solution, and the solvent evaporated to give a colorless solid. The ^{1}H n.m.r. spectrum of this material showed the presence of 4 and 32 only, in relative proportions 61% and 39%, respectively.

Reaction of 2-Hydroxyethanesulfonyl Chloride (1) with Pyridine in Methylene Chloride

(a) The sulfonyl chloride (1) (0.50 g, 3.45×10^{-3} mol) was dissolved in methylene chloride (40 mL) at room temperature. Pyridine (2.8 mL, 3.5×10^{-2} mol) was injected into the solution with magnetic stirring. After approximately ten seconds a colorless precipitate was observed. After one hour the precipitate was filtered (0.395 g, 61%). The ^{1}H n.m.r. spectrum of this material was identical to that of an authentic specimen of N-pyridinium 2-ethanesulfonate (pyridine betaine) (34). The filtrate was evaporated, and the excess pyridine removed by azeotroping with toluene. The colorless solid residue was dissolved in water (~2 mL) and eluted down a column of Rexyn 101 (H^+) until the eluant was no longer acidic towards pH paper. The solvent was evaporated to yield a pale yellow oil (0.170 g) whose ^{1}H n.m.r. spectrum (D_2O) indicated the presence of 2-chloroethanesulfonic acid (25%) and ethenesulfonic acid (13%) in a 2:1 relative ratio (determined by integration of the methylene absorptions of the sulfonic acids), and a trace amount (1%) of isethionic acid. These products were identified by comparison with ^{1}H n.m.r. spectra of authentic specimens.

(b) In a separate experiment the sulfonyl chloride (1) (0.30 g, 2.08×10^{-3} mol) was dissolved in methylene chloride (25 mL) and treated with pyridine (1.7 mL, 2.11×10^{-2} mol). After 2 hours the precipitate was filtered off (0.195 mg, 50%). The filtrate was evaporated under reduced pressure to give an oil (0.215 g) whose ^{1}H n.m.r. spectrum ($CDCl_3$) indicated the presence of pyridinium 2-chloroethanesulfonate (36) (34%) and pyridinium ethenesulfonate (37) (10%), with a trace

amount (1%) of pyridinium isethionate (35). The products were identified by comparison with ^1H n.m.r. spectra of authentic specimens.

Preparation of Pyridinium 2-Chloroethanesulfonate (36)

Freshly recrystallized sodium 2-chloroethanesulfonate (32) (1.0 g, 6.00×10^{-3} mol, recrystallized from 95% alcohol) was dissolved in water (10 mL) and added to a short column of Rexyn 101 (H^+) strong acid resin. The column was then eluted with water until the eluant was no longer acidic towards pH paper. Pyridine (0.5 mL, 6.22×10^{-3} mol) was added to the solution, and the solvent was evaporated to yield a red solid (1.3 g, 90%). Recrystallization from absolute alcohol gave a colorless hygroscopic solid, m.p. 62 - 65°; ^1H n.m.r. (D_2O) δ: 3.36 (t, 2H), 3.90 (t, 2H), 8.12 (t, 2H), 8.68 (m, 1H), 8.84 (m, 2H); ($CDCl_3$) δ: 3.34 (t, 2H), 3.93 (t, 2H), 8.15 (t, 2H), 8.63 (m, 1H), 9.03 (m, 2H).

Preparation of Pyridinium 2-Hydroxyethanesulfonate (Pyridinium Isethionate) (35)

Sodium isethionate (4) (2.5 g, 1.8×10^{-2} mol) was dissolved in water (5 mL) and added to a short column of Rexyn 101 (H^+). Elution of the column with water, followed by evaporation of the solvent gave a colorless syrup. Pyridine (2 mL, 2.7×10^{-2} mol) was added and the excess pyridine evaporated to give a light syrup which crystallized on standing (3.0 g, 80%), m.p. 68 - 72°; ^1H n.m.r. (D_2O) δ: 3.17 (t, 2H), 3.96 (t, 2H), 8.09 (t, 2H), 8.64 (m, 1H), 8.78 (d, 2H); (T-60, $CDCl_3$) δ: 3.1 (m, 2H), 4.0 (m, 2H), 7.8 (m, 2H), 8.2 (m, 1H), 8.7 (m, 2H).

Preparation of Pyridinium Ethenesulfonate (37)

Recrystallized sodium ethenesulfonate (33) (1.15 g, 8.9×10^{-3} mol, recrystallized from 95% alcohol) was dissolved in water (~2 mL) and added to a short column of Rexyn 101 (H^+). The column was eluted with water until the eluant was not longer acidic towards pH paper. Pyridine (0.75 mL, 9.3×10^{-3} mol) was added to this solution, and the solvent evaporated to yield a hygroscopic pale yellow solid; ^{1}H n.m.r. ($CDCl_3$) δ: 5.30 (d of d, 1H), 5.80 (d of d, 1H), 6.50 (m, 1H), 7.82 (t, 2H), 8.35 (m, 1H), 8.8 (d, 2H); (CD_3NO_2) δ: 5.60 (d of d, 1H), 5.92 (d of d, 1H), 6.67 (m, 1H), 8.14 (t, 2H), 8.64 (m, 1H), 8.92 (d of d, 2H).

Control Experiment

Pyridinium 2-chloroethanesulfonate (36) (0.14 g, 6.3×10^{-4} mol), pyridinium ethenesulfonate (37) (0.025 g, 1.3×10^{-4} mol), pyridinium isethionate (35) (0.11 g, 5.4×10^{-4} mol), pyridinium chloride (0.10 g, 8.2×10^{-4} mol) and pyridine (0.4 mL, 5.0×10^{-3} mol) were dissolved in methylene chloride (25 mL) at room temperature. After standing for 3 hours (no precipitate was observed) the solvent was evaporated. The ^{1}H n.m.r. spectrum ($CDCl_3$) of the residue showed 35, 36 and 37 in the same relative proportions as the original mixture.

Preparation of 2-Chloroethanesulfonic Acid

Sodium 2-chloroethanesulfonate (32) (1.0 g, 6.0×10^{-3} mol) was dissolved in water (~5 mL) and eluted down a column of Rexyn 101 (H^+)

resin with water until the eluant was no longer acidic towards pH paper. Evaporation of the solvent under reduced pressure gave 2-chloroethanesulfonic acid (0.80 g, 93%) as a light yellow oil; ^{1}H n.m.r. (D_2O) δ: 3.34 (t, 2H), 3.86 (t, 2H).

Preparation of 2-Hydroxyethanesulfonic (Isethionic) Acid

Sodium 2-hydroxyethanesulfonate (4) was treated with Rexyn 101(H^+) strong acid resin in the manner described above to yield 2-hydroxyethanesulfonic acid as a colorless crystalline solid; ^{1}H n.m.r. (D_2O) δ: 3.16 (t, 2H), 3.95 (t, 2H).

Reaction of 2-Hydroxyethanesulfonyl Chloride (1) with Pyridine in Deuterium Oxide at 25.0°C

The sulfonyl chloride (1) (0.330 g, 7.27×10^{-3} mol) was added to a stirred solution of pyridine (2.0 mL, 2.49×10^{-2} mol) in D_2O (50 mL) maintained at 25.0° and apparent pH 6.0 with 2.2 M sodium deuteroxide titrant (prepared ~~from~~ sodium and D_2O). After 30 minutes the pH was adjusted to 7.5 and the solution extracted with ether (4 × 30 mL). The aqueous layer was evaporated under reduced pressure to yield a colorless solid. The ^{1}H n.m.r. spectrum (D_2O) of this material showed absorptions at δ: 3.0 - 4.0, 5.0, 5.8 - 7.0, 8.0 - 9.0 ppm, indicating the presence of pyridine betaine (34), sodium 2-chloroethanesulfonate (32), sodium 2-hydroxyethanesulfonate (4), sodium ethenesulfonate (33). The relative proportions of these products were estimated (by ^{1}H n.m.r. integration) to be 57%, 7%, 33%, 3% respectively. No deuterium was observed in any of the products except 4, which was estimated to be roughly 50%

monodeuterated at the alpha carbon (by integration of the absorptions at δ: 3.12, 3.90 ppm).

Control Experiment

Sodium Isethionate (4), Sodium 2-Chloroethanesulfonate (32), Pyridine Betaine (34) with Pyridine in Deuterium Oxide

A mixture of sodium isethionate (4) (0.110 g, 7.4×10^{-4} mol), sodium 2-chloroethanesulfonate (32) (0.038 g, 2.3×10^{-4} mol) and pyridine betaine (34) (0.075 g, 4.0×10^{-4} mol) was dissolved in D_2O (30 mL) and the relative proportions confirmed by ^1H n.m.r. spectroscopy. Pyridine (1.0 mL, 1.2×10^{-2} mol) was added to this solution at room temperature. The apparent pH was adjusted to 6.0 with 20% DCl/D_2O solution. After standing for 30 minutes the pH was adjusted to 7.0 with 0.1 M sodium deuteroxide solution. The solution was extracted repeatedly with ether. Evaporation of the aqueous layer gave a residue whose ^1H n.m.r. spectrum (D_2O) showed 4, 32 and 34 in the same relative proportions as in the starting mixture, with no other observed products.

General Procedure for Reactions of 2-Hydroxyethanesulfonyl Chloride (1) with Tertiary Amines in Methylene Chloride in the Presence of Primary Alcohols

In a series of experiments 2-hydroxyethanesulfonyl chloride (1) (∿0.500 g, 3.45×10^{-3} mol) was dissolved in methylene chloride (∿40 mL) containing either excess 1-butanol (Fisher) or neopentyl alcohol (Aldrich). A tertiary amine base was then injected with stirring into the solution at room temperature. When pyridine or trimethylamine (Eastman) was

employed, a precipitate was observed within the first 5 minutes of the reaction. The mixture was worked up by extraction with water (1 × 40 mL). The methylene chloride layer was dried, filtered and the solvent evaporated to yield an oil whose composition was determined by ^{1}H n.m.r. spectroscopy. In all experiments, the oil consisted of two sulfonate esters, a 2-hydroxyethanesulfonate ester and an ethenesulfonate ester. These products were identified by comparison with ^{1}H n.m.r. spectra of authentic specimens. In one reaction a sample of authentic neopentyl ethenesulfonate (43) was added to an n.m.r. tube containing the crude reaction mixture of esters, with the resulting enhancement of the absorptions attributed to the amount of 43 already present.

The aqueous extract was evaporated under reduced pressure, and the residue dissolved in water (1 - 2 mL). This solution was added to a short column of Rexyn 101 (H^+), and the column eluted with water until the eluant was no longer acidic towards pH paper. The eluant was then evaporated, and the residue triturated repeatedly with anhydrous ether (5 × 30 mL). These ether extracts were combined and evaporated to give an oil, whose composition was investigated by ^{1}H n.m.r. spectroscopy (D_2O). The spectrum showed absorptions in the region δ: 3.0 - 4.0 ppm, indicating the presence of isethionic acid and 2-chloroethanesulfonic acid (identified by comparison with ^{1}H n.m.r. spectra of the authentic specimens of the acids).

The ^{1}H n.m.r. spectrum (D_2O) of the residue which was insoluble in ether was identified as the amine betaine corresponding to the amine employed in the reaction with 1, by comparison with the ^{1}H n.m.r. spectra of the authentic materials.

Reaction of 2-Hydroxyethanesulfonyl Chloride (1) with 1-Butanol-O-d and Trimethylamine in Methylene Chloride

Following the general procedure given above, the sulfonyl chloride (1) (0.500 g, 3.45×10^{-3} mol) was treated with trimethylamine (~0.5 mL, 6×10^{-3} mol) and 1-butanol-O-d (Merck, Sharp, Dohme Ltd., 99 Atom % D) (2.65 g, 3.5×10^{-2} mol) in dry methylene chloride (40 mL). After one hour at room temperature, the reaction was worked up as described above. The reaction products were observed to be butyl 2-hydroxyethanesulfonate (39) (40%), butyl ethenesulfonate (41) (3%), 2-chloroethanesulfonic acid (14%), trimethyl betaine (38) (40%) and isethionic acid (3%). Only 39 was observed to have incorporated deuterium, and was estimated (by ^{1}H n.m.r. integration of the methylene absorptions at δ: 4.27, 3.34 ppm) to be ≥80% monodeuterated at the carbon alpha to the sulfonate group.

Isolation of Butyl 2-Hydroxyethanesulfonate (39)

A crude mixture of butyl ethenesulfonate (41) and butyl 2-hydroxyethanesulfonate (39) (obtained from a reaction of 2-hydroxyethanesulfonyl chloride (1) with trimethylamine and 1-butanol) was triturated repeatedly with hexanes. The ^{1}H n.m.r. and i.r. spectra of the residue found to be insoluble in hexanes were identical with those of an authentic specimen of 39 prepared by an independent route (42); ^{1}H n.m.r. ($CDCl_3$) δ: 0.96 (t, 3H), 1.24 - 1.93 (m, 4H), 2.56 (s, 1H), 3.35 (t, 2H), 4.08 (br q, 2H), 4.28 (t,2H).

Isolation of 2,2-Dimethylpropyl-2'-Hydroxyethanesulfonate (Neopentyl 2-Hydroxyethanesulfonate) (40)

This sulfonate ester (40) was isolated by performing a cold finger distillation under reduced pressure (0.002 mm Hg, oil bath temperature 90°) of a crude mixture of the two sulfonate esters obtained from a reaction of 2-hydroxyethanesulfonyl chloride (1) with trimethylamine and neopentyl alcohol, to yield a colorless oil; ^{1}H n.m.r. ($CDCl_3$) δ: 1.01 (s, 9H), 2.78 (bs, 1H), 3.37 (t, 2H), 3.93 (s, 2H), 4.09 (t, 2H); i.r. (CH_2Cl_2) 3610 (w), 2970 (m), 1353 (s), 1160 (s), 1058 (m), 900 (vs), 937 (s) cm^{-1}; Anal. calcd. for $C_7H_{16}O_4S$: C, 42.68; H, 8.24; S, 16.30. Found: C, 42.84; H, 8.22; S, 16.34.

Preparation of Butyl 2-Acetoxyethanesulfonate

Butyl 2-hydroxyethanesulfonate (39) (0.100 g, 5.52×10^{-4} mol) was dissolved in $CDCl_3$ (0.5 mL) and placed in an n.m.r. tube. Acetyl chloride (Fisher) (0.5 mL, 7.0×10^{-3} mol) was added and the solution left overnight. Evaporation of the solvent gave an oil which was distilled in a cold finger apparatus under reduced pressure (0.5 mm Hg, bath temperature 120°) to give a colorless oil. This material was dissolved in methylene chloride (~1 mL) and eluted down a short column of silica gel (BDH, 35 - 70 mesh) using methylene chloride. Evaporation of the solvent gave a colorless oil (0.070 g, 53%); Anal. calcd. for $C_8H_{16}O_5S$: C, 42.84; H, 7.19; S, 14.30. Found: C, 42.78; H, 7.02; S, 14.38. ^{1}H n.m.r. ($CDCl_3$) δ: 0.96 (t, 3H), 1.20 - 1.90 (m, 4H), 2.10 (s, 3H), 3.44 (t, 2H), 4.49 (t, 2H); i.r. (CH_2Cl_2) 3060 (w), 2965 (m), 2935 (m), 1750 (s), 1360 (s), 1255 (s), 1165 (s), 1050 (m),

1038 (m), 938 (s), 910 (m), 888 (m) cm^{-1}.

Preparation of N,N,N-Triethylammoniumethanesulfonate (Triethyl Betaine) (43)

Triethylamine (Eastman) (1.4 mL, 1.0×10^{-2} mol) was injected into a solution of sodium 2-bromoethanesulfonate (50) (2.0 g, 9.5×10^{-3} mol) in water (40 mL). The solution was allowed to stand at room temperature for 11 days. Evaporation of the solvent gave a colorless solid which was dissolved in water (~2 mL), added to a short column of Rexyn 300 (H-OH) resin and eluted with water. Evaporation of the solvent gave a colorless crystalline solid (0.075 g, 35%), which decomposed >280°; Anal. calcd. for $C_8H_{19}NO_3S$: C, 45.91; H, 9.15; N, 6.69; S, 15.32. Found: C, 46.03; H, 9.31; N, 6.81; S, 15.36; ^1H n.m.r. (D_2O) δ: 1.32 (t, 9H), 3.43 (m, 10H); i.r. (nujol) 1270 (w), 1238 (m), 1213 (s), 1195 (s), 1155 (w), 1040 (s) cm^{-1}.

N,N,N-Trimethylammoniumethanesulfonate (Trimethyl Betaine) (38)

This compound was prepared according to the method of Stevens (50) from 2-bromoethanesulfonate and trimethylamine; ^1H n.m.r. (D_2O) δ: 3.20 (s, 9H), 3.45 (m, 2H), 3.74 (m, 2H).

Isolation of N-Quinuclidiniumethanesulfonate (Quinuclidine Betaine) (44)

The crude betaine (44) was isolated from a reaction of the sulfonyl chloride (1) with quinuclidine (Aldrich) and 1-butanol. The betaine (44) was recrystallized from absolute alcohol to yield a colorless solid, decomp. >390°; Anal. calcd. for $C_9H_{17}NO_3S$: C, 49.29; H, 7.81; N, 6.39;

S, 14.62. Found: C, 49.29; H, 7.89; N, 6.44; S, 14.71. ^{1}H n.m.r. (D_2O) δ: 1.82 - 2.33 (m, 7H), 3.20 - 3.68 (m, 10H); i.r. (nujol) 1277 (m), 1187 (s), 1112 (m), 1040 (s), 792 (m) cm^{-1}.

Preparation of Trimethylammonium 2-Chloroethanesulfonate

Sodium 2-chloroethanesulfonate (32) (∿5.0 g, 3.0×10^{-2} mol, recrystallized from absolute alcohol) was dissolved in water (∿10 mL) and added to a column of Rexyn 101 (H^+). The column was eluted with water until the eluant was no longer acidic towards pH paper. The solution was then treated with an excess of trimethylamine, and the solvent evaporated to yield a colorless crystalline solid (3.6 g, 60%), m.p. 84 - 87°; ^{1}H n.m.r. (D_2O) δ: 2.87 (s, 9H), 3.25 (t, 2H), 3.80 (t, 2H). The salt was used without further purification in the following control experiment.

Control Experiments

(a) A solution of triethylammonium 2-chloroethanesulfonate (0.130 g, 6.4×10^{-4} mol), trimethyl betaine (38) (0.113 g, 6.8×10^{-4} mol), trimethylammonium chloride (0.210 g, 2.2×10^{-3} mol) and 1-butanol (∿1.0 mL, 1.0×10^{-2} mol) in water (50 mL) was prepared at room temperature. The solvent was evaporated under reduced pressure to yield a colorless solid. This residue was dissolved in water (∿3 mL) and added to a short column of Rexyn 101 (H^+) resin. The column was eluted with water until the eluant was no longer acidic towards pH paper. The solvent was evaporated and the residue triturated with ether (7 × 30 mL). Evaporation of the ether gave a residue (0.090 g) whose ^{1}H n.m.r. spectrum

(D_2O) of the material insoluble in ether (0.10 g) showed only the presence of trimethyl betaine (38).

(b) A mixture of pyridine betaine (34) (0.052 g, 2.8×10^{-4} mol), neopentyl alcohol (0.600 g, 6.8×10^{-3} mol), pyridinium chloride (0.140 g, 1.2×10^{-3} mol), sodium 2-chloroethanesulfonate (32) (0.180 g, 1.08×10^{-3} mol), sodium 2-hydroxyethanesulfonate (4) (0.190 g, 1.28×10^{-3} mol) was dissolved in water (40 mL) at room temperature. The solvent was evaporated under reduced pressure and the residue dissolved in water (~2 mL). This solution was added to a short column of Rexyn 101 (H^+) and eluted with water as described earlier. The water was evaporated and the residue triturated repeatedly with anhydrous ether. The ether extracts were combined and evaporated to give a yellow oil (0.290 g). The ^1H n.m.r. spectrum (D_2O) of this material showed absorptions in the region δ: 3.0 - 4.0 ppm indicating the presence of 2-chloroethanesulfonic acid and 2-hydroxyethanesulfonic acid, in relative proportions 47% and 53% respectively. The ^1H n.m.r. spectrum of the material insoluble in ether (0.073 g) showed peaks corresponding to an equimolar amount of isethionic acid and pyridine betaine (34). The overall relative proportions of the two sulfonic acids were not significantly different from the relative proportions of 4 and 33 initially present in the mixture.

Reaction of Butyl 2-Hydroxyethanesulfonate (39) with Trimethylamine and 1-Butanol in Methylene Chloride

Butyl 2-hydroxyethanesulfonate (39) (0.077 g, 4.3×10^{-4} mol) was combined with 1-butanol (0.320 g, 4.30×10^{-3} mol) in methylene chloride (30 mL) at room temperature. Trimethylamine (~0.5 mL, 6×10^{-3} mol)

was added with stirring. After one hour the organic layer was extracted once with water (30 mL). The organic layer was dried, filtered and the solvent removed to yield an oil (0.061 g, 79%) whose ^{1}H n.m.r. spectrum ($CDCl_3$) showed it to be the starting ester (39). The aqueous layer was evaporated, and the residue eluted down a column of Rexyn 101 (H^+) until the eluant was no longer acidic towards pH paper. Evaporation of the solvent yielded an oil (0.011 g) whose ^{1}H n.m.r. spectrum (D_2O) indicated the presence of trimethyl betaine (38) (2%) and isethionic acid (16%).

Control Experiment

Neopentyl 2-Hydroxyethanesulfonate (40) with Triethylamine, Triethylammonium Chloride and Neopentyl Alcohol in Methylene Chloride

Neopentyl 2-hydroxyethanesulfonate (40) (0.090 g, 4.6×10^{-4} mol). neopentyl alcohol (0.350 g, 4.0×10^{-3} mol), and triethylammonium chloride (0.080 g, 5.9×10^{-4} mol) were dissolved in methylene chloride (30 mL) at room temperature. Triethylamine (0.100 mL, 7.2×10^{-4} mol) was added, and the solution allowed to stand for 1 hour. The solution was extracted with water (1 × 30 mL) and the organic layer dried, filtered, and the solvent removed to yield a pale yellow oil (0.075 g). The ^{1}H n.m.r. spectrum ($CDCl_3$) of this oil indicated only the presence of 40, with no sign of any absorptions corresponding to neopentyl ethenesulfonate (42).

Control Experiment

Neopentyl Ethenesulfonate (42) with Triethylamine, Triethylammonium Chloride and Neopentyl Alcohol

Neopentyl ethenesulfonate (42) (0.088 g, 4.6×10^{-4} mol) triethylammonium chloride (0.060 g, 4.4×10^{-4} mol) and neopentyl alcohol (0.050 g, 5.7×10^{-4} mol) were dissolved in $CDCl_3$ (1.0 mL) at room temperature. Triethylamine (Eastman) (0.20 mL, 1.5×10^{-3} mol) was added. After 24 hours the ^1H n.m.r. spectrum of this solution showed no observable reaction.

APPENDIX 1

Symbols Employed for Rate Constants in Chapter 1

(a) Empirical Rate Constants

k_ψ: the observed pseudo first order rate constant for the solvolysis of the sulfonyl chloride in the presence or absence of added bases.

k_1: the pseudo first order rate constant for the uncatalysed solvolysis of the sulfonyl chloride.

k_B: the second order rate constant for the reaction of the sulfonyl chloride with the pyridine base.

k_{H_2O}: the second order rate constant for the reaction of water with the sulfonyl chloride (= $k_1/55.5$ M).

k_{OH^-}: the second order rate constant for the reaction of the sulfonyl chloride with hydroxide ion.

k_D: the rate constant for the S_N2 attack of water upon the sulfonyl chloride (= k_1 (% ethenesulfonate product)).

k_C: the rate constant for the S_N2' attack of water upon the sulfonyl chloride (= k_1 (% 2-hydroxyethanesulfonate)).

(b) Mechanistic Rate Constants

k_N: second order rate constant for attack of pyridine on carbon in mechanism (c), Scheme 1.15.

k_S: second order rate constant for attack of pyridine on sulfur in mechanism (c), Scheme 1.15.

k_H: rate constant for protonation of the zwitterion intermediate in the generation of the betaine product in Scheme 1.16.

k_E: rate constant for elimination of the substituted pyridine base from the zwitterion to form the ethenesulfonate product in Scheme 1.16.

K_1: equilibrium constant for pre-association of the pyridine base with the sulfonyl chloride in Scheme 1.17.

k_2: second order rate constant for reaction of the pyridine base with the sulfonyl chloride from the pre-associated complex in Scheme 1.17.

APPENDIX 2

Correction Applied to Observed Equilibrium Constants for Weak Pyridine Bases

The hydrolysis of conjugate acids of very weak bases may occur when bases of $pK_a \leq 4$ are titrated (1).

$BH^+ + H_2O \rightleftharpoons B + H_3^+O$ where $[B]$ = concentration of free base and $[BH^+]$ = concentration of protonated base.

$$K_a = \frac{[B][H_3^+O]}{[BH^+]}$$

When B is a very weak base (and therefore BH^+ is a relatively strong acid) then at the observed pK_a of the base, more than half of the total base is in the free form.

If X = extra conc. of free base at this point, then

$$K_a' = \frac{[(B_T/2) + X][X]}{[(B_T/2) - X]}$$

where $[B_T]$ = conc. of total base present.
K_a' = practical dissociation constant.

$$\therefore \quad X^2 + X(B_T/2 + K_a) - K_a(B_T/2) = 0$$

Solving for X, one can then calculate the correction to the observe pK_a:

$$\text{correction} = \log \frac{[B_T/2 + X]}{[B_T/2 - X]}$$

The magnitude of the corrections determined for the pyridine bases utilized were in the range 0.01 - 0.03 pK_a.

An equivalent means of calculating the practical dissociation constant (pK_a') is described by D.D. Perrin (2) for hydrochloric acid titration of a weak base.

$$pK_a = pH + \log\left(\frac{[Cl^-] + [OH^-] + [H^+]}{[B_T] + [H^+] - [Cl^-] - [OH^-]}\right) - \log\frac{f_B}{f_\pm}$$

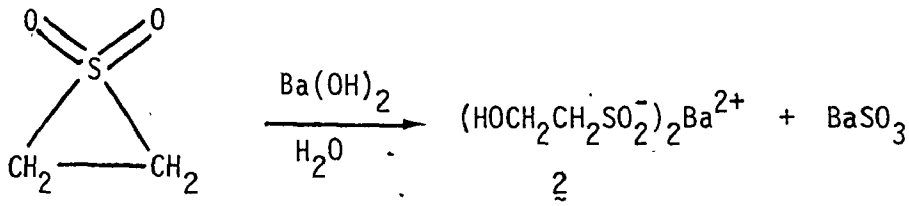
where f_B = activity coefficient for base

$f_\pm$ = mean ionic activity coefficient

If the activity coefficients are ignored then the practical dissociation constant (pK_a') is obtained.

APPENDIX 3

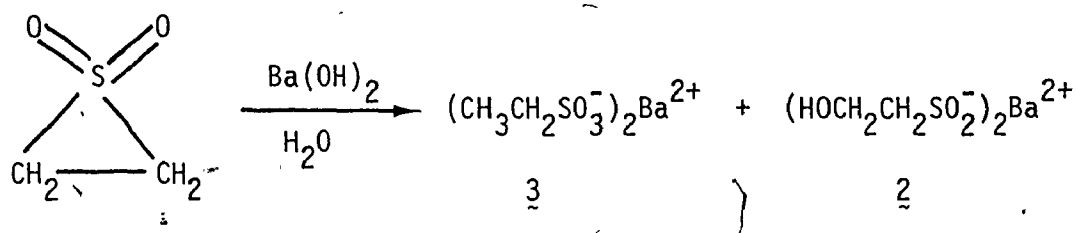
During the synthetic attempts towards the preparation of 2-hydroxyethanesulfonyl chloride (see Chapter 4), a portion of the work of Hesse, Reichold and Majumdar (1) was repeated. These authors claimed the following reaction of ethylene sulfone (1).



1

2

Since this reaction to generate the sulfinate salt (2) was potentially valuable if 2 could be transformed into the desired hydroxyethanesulfonyl chloride, it was repeated under the conditions described by Hesse et al. The products of the reaction however, were observed to be mainly barium ethanesulfonate (3) with only a trace (4% relative proportion) of the sulfinate (2)



3 2

The reaction was apparently a slow one since a large proportion (~40%) of the mixture was comprised of unreacted ethylene sulfone (1). The ethanesulfonate salt (3) was identified by conversion to ethanesulfon-p-toluidide. The ^1H n.m.r., i.r. spectra of this derivative were identical with those of an authentic specimen (2).

An authentic specimen of barium 2-hydroxyethanesulfinate (2) was kept at 98° for 5 hours with only a 1% loss in weight, contrary to the results of Hesse et al (1), who reported the rapid decomposition of 2 into ethylene and barium sulfite at room temperatures above 50°.

$$\underset{2}{(HOCH_2CH_2SO_2^-)_2Ba^{2+}} \xrightarrow{\Delta} CH_2{=}CH_2 + BaSO_3$$

While sodium 2-chloroethanesulfinate (3) has been established by Kempe and Norin (3) to rapidly decompose to ethylene, sulfur dioxide and sodium chloride at 60°, the ease of this reaction may be due to the reasonable nucleofugality of chloride ion.

$$\underset{3}{ClCH_2CH_2SO_2^-Na^+} \xrightarrow{\Delta} CH_2{=}CH_2 + SO_2 + NaCl$$

Hydroxide ion is generally regarded as a poor nucleofuge, certainly much poorer than chloride ion. Therefore the report of Hesse et al of the facile decomposition of 2 at this temperature was suspect, and 2 has now been shown to be stable at least up to ~100°.

The source of ethylene in the experiments of Hesse may have been the decomposition of unreacted ethylene sulfone (1).

Ethylene Sulfone (1)

Ethylene sulfone (1) was prepared by the method of Hesse and Majumdar (1) using diazomethane prepared from nitrosomethylurea (Aldrich) and potassium hydroxide solution. The crystalline solid obtained in this manner had m.p. 18 - 19°; ^{1}H n.m.r. ($CDCl_3$) δ: 3.16 (s); i.r. ($CHCl_3$) 3102 (s), 3030 (s), 1389 (s), 1375 (vs), 1170 (vs, 1005 (m), 445 (s) cm^{-1}.

Reaction of Ethylene Sulfone (1) with Barium Hydroxide

A mixture of barium hydroxide·8 H_2O (2.0 g, 6.3×10^{-3} mol) in water (100 mL) was combined with ethylene sulfone (1) (0.500 g; 5.4×10^{-3} mol) at room temperature. After stirring for 24 hours, the mixture was filtered and the solvent evaporated under reduced pressure (bath temperature $\leq 35^{\circ}$) to give a colorless solid ($\sim$1.2 g). The ^1H n.m.r. spectrum (D_2O) of this material indicated the presence of unreacted sulfone (1), barium ethanesulfonate (3) and barium 2-hydroxyethanesulfinate (2), in reltiave proportions (as determined by integration of the n.m.r. spectrum) of 43%, 53%, 4% respectively. The mixture was dissolved in water and continuously extracted with methylene chloride for 24 hours. The aqueous layer was then passed through a column of Rexyn 101 (H^+), and the solvent evaporated to yield a brown syrup. Thionyl chloride (Fisher, 50 mL) was added along with a few drops of N,N-dimethylformamide (Fisher). After refluxing for 3 days, the excess thionyl chloride was evaporated to give a brown oil (0.40 g). To this oil a solution of p-toluidine (BDH) (0.50 g, 4.7×10^{-3} mol) and triethylamine (1.0 mL, 7.2×10^{-3} mol) in benzene (15 mL) was added. After standing overnight the solution was extracted with 1.0 N HCl (2 × 10 mL) and water (10 mL). The benzene layer was dried, filtered and the solvent evaporated to yield a brown oil (0.160 g). The oil was crystallized and recrystallized from benzene: 60 - 80° petroleum ether to yield off-white crystals (10 mg); m.p. 79 - 80°; mixed m.p. with authentic sample gave no depression; ^1H n.m.r., i.r. spectra identical to an authentic specimen of ethanesulfon-p-toluidide.

Ethanesulfon-p-Toluidide

Ethanesulfon-p-toluidide was prepared by the method of Beatson (2) from ethanesulfonyl chloride (Eastman) and p-toluidine (BDH), m.p. 79 - 80°.

Preparation of Barium Ethanesulfonate (3)

Ethanesulfonyl chloride (1.0 g, 7.8×10^{-3} mol) was combined with a mixture of barium hydroxide·8 H_2O (2.3 g, 7.3×10^{-3} mol) in water (100 mL). The mixture was stirred at room temperature for 3 hours, then the solvent was removed under reduced pressure. The off-white residue (~2.0 g) was recrystallized from 95% alcohol to give colorless needles (m.p. >395°); ^{1}H n.m.r. (D_2O) δ: 1.29 (t, 3H), 2.94 (q, 2H); i.r. (nujol) 1255 (m), 1187 (s), 1162 (s), 1052 (s), 784 (m), 1220 (w), 575 (m) cm^{-1}.

Stability of Barium 2-Hydroxyethanesulfinate (2)

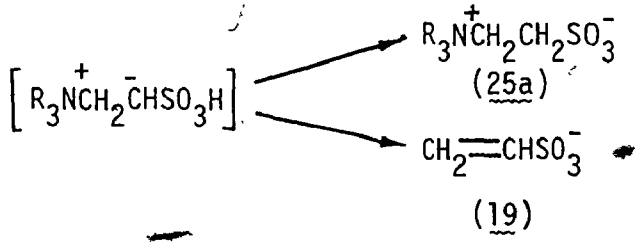
Barium 2-hydroxyethanesulfinate (2) (0.049 g, 1.4×10^{-1} mol) prepared as described in Chapter 4 (by reaction of 2-hdyroxyethanesulfinic acid with barium hydroxide) was kept at 98° (using a water bath) for 5 hours. At the end of this time a weight loss of 1% was recorded.

APPENDIX 4

Isotope Effect for Reaction of Pyridine with Ethenesulfonyl Chloride in Water and Deuterium Oxide at 25.0°C

(a) In Water

From Scheme 1.16:



(25a)

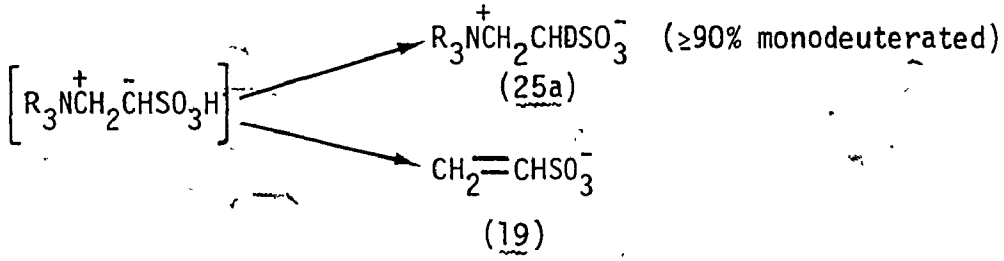
(19)

% betaine (25a): 80%

% $CH_2{=}CHSO_3^-$ (19): 20%

$$\therefore \quad \frac{k_{1H}}{k_2} = 4.0$$

(b) In Deuterium Oxide



(≥90% monodeuterated)

(25a)

(19)

% betaine: 70%; % (19): 30%

$$\therefore \quad \frac{k_{1D}}{k_2} = 2.3$$

$$\frac{0.9\ k_{1D} + 0.1\ k_{1H}}{k_2} = 2.3$$

$$\frac{0.9\ k_{1D}}{k_2} + \frac{0.1\ k_{1H}}{k_2} = 2.3$$

$$\frac{0.9\ k_{1D}}{k_2} = 1.9$$

$$\frac{k_{1D}}{k_2} = 2.1$$

Then assuming k_2 in water = k_2 in D_2O:

$$\text{isotope effect } \left(= \frac{k_{1H}}{k_{1D}}\right) = \frac{4.0}{2.1}$$

$$= 1.9 \text{ (if the betaine is 90\% } \alpha \text{ monodeuterated).}$$

If the betaine is 100% α monodeuterated, then isotope effect $= \frac{4.0}{2.3}$

$$= 1.7$$

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